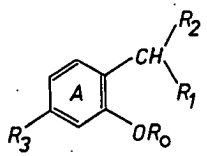
(12)UK Patent Application (19)GB (11) 2 109 373 A

(21) Application No 8230352
(22) Date of filing
26 Oct 1982
(30) Priority data
(31) 6883/81
(32) 28 Oct 1981
(33) Switzerland (CH)
(43) Application published
2 Jun 1983
(51) INT CL³ C07D 295/14
A61K 31/40 31/195
31/445 31/535
C07C 101/72 101/453
103/28 103/76
103/85
C07D 207/327 209/08
295/10
(52) Domestic classification
C2C 1340 1341 1343
1532 1562 213 215
220 226 227 22Y 246
250 251 255 25Y 282
28X 292 29Y 304 305
30Y 313 314 31Y 321
323 32Y 338 342 34Y
351 355 360 363 364
365 366 367 368 36Y
37X 388 401 407 40Y
43X 490 491 500 502
509 50Y 574 593 594
620 623 624 625 628
62X 638 652 658 65X
660 662 66X 675 699
802 80Y AA BG BL KH
KQ LT UH UJ
U1S 1322 1323 1326
1342 C2C
(56) Documents cited
GB 1198212
(58) Field of search
C2C
(71) Applicant
Ciba Geigy AG
(Switzerland)
Klybeckstrasse 141
4002 Basle
Switzerland
(72) Inventors
Paul Wenk
Werner Breitenstein
Marcus Baumann
(74) Agent and/or Address for Service
Thomas Sharman
Ciba-Geigy PLC
Patent Department
Tenax Road
Trafford Park
Manchester M17 1WT

(54) **Aminophenol acetic acid**

(57) The invention relates to novel phenol derivatives, especially those of the general formula



(I),

in which R_0 represents hydrogen or an acyl radical, R_1 represents carboxy, esterified carboxy or amidated carboxy, R_2 represents hydrogen or an aliphatic radical, R_3 represents an amino group di-substituted by two monovalent radicals or by one divalent radical, and the aromatic ring A may be additionally substituted, and their salts and isomers, processes for the manufacture of compounds of the formula (I) and their salts and isomers, pharmaceutical preparations containing these compounds, and their use as the active ingredients of medicaments and/or for the manufacture of pharmaceutical preparations.

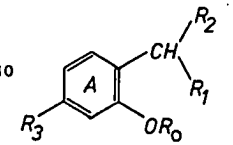
GB 2 109 373 A

The chemical formulas appearing in the printed specification were submitted after the date of filing, the formulas originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

Phenol derivatives

The invention relates to novel phenol derivatives, especially those of the general formula



(I),

in which R_0 represents hydrogen or an acyl radical, R_1 represents carboxy, esterified carboxy or amidated carboxy, R_2 represents hydrogen or an aliphatic radical, R_3 represents an amino group di-substituted by two monovalent hydrocarbon radicals or by one divalent hydrocarbon radical, and the aromatic ring A may be additionally substituted, and their salts and isomers, processes for the manufacture of compounds of the formula (I) and their salts and isomers, pharmaceutical preparations containing these compounds, and their use as the active ingredients of medicaments and/or for the manufacture of pharmaceutical preparations.

An aliphatic radical R_2 is especially saturated and unsubstituted and represents, especially, a lower alkyl radical.

An acyl radical is, for example, a lower alkanoyl radical or an aryl-lower alkanoyl radical, such as a phenyl-lower alkanoyl radical that is unsubstituted or mono- or poly-substituted in the phenyl moiety wherein, when substituted, phenyl may contain, for example, one or more of the following substituents: an aliphatic radical, such as lower alkyl, lower alkenyl, optionally branched, especially bridging two carbon atoms, 3- or 4-membered alkylene having from 3 to 8 carbon atoms, hydroxy-lower alkyl or halo-lower alkyl, lower alkoxy, lower alkylthio, lower alkanesulphinyl, lower alkanesulphonyl, hydroxy, lower alkanoyloxy, lower alkanoyl, halogen and nitro.

An aryl-lower alkanoyl radical is deriving more especially from a phenyl-lower alkanecarboxylic acid of the formula (I), R_0 being preferable hydrogen, furthermore lower alkanoyl and the radicals R_2 and R_3 as well as the substituents of the ring A having the meanings given for compounds of the formula (I), preferably the same.

Esterified carboxy is, for example, carboxy esterified by an aliphatic or aromatic alcohol. There comes into consideration as aliphatic alcohol, for example, a lower alkanol or a lower alkanol substituted, for example, by hydroxy, by lower alkoxy, by lower alkanoyloxy or by aryl, such as substituted or unsubstituted phenyl wherein, when substituted, phenyl may contain, for example, one or more of the following substituents: an aliphatic radical, such as lower alkyl, lower alkonyl, optionally branched, especially bridging two carbon atoms, 3- or 4-membered alkylene having from 3 to 8 carbon atoms, hydroxy-lower alkyl or halo-lower alkyl, lower alkoxy, lower alkylthio, lower alkanesulphinyl, lower alkanesulphonyl, hydroxy, lower alkanoyloxy, lower alkanoyl, halogen and nitro.

There comes into consideration as aromatic alcohol, for example, substituted or unsubstituted phenol wherein, when substituted, phenol may contain, for example, one or more of the following substituents: an aliphatic radical, such as lower alkyl, lower alkenyl, optionally branched, especially bridging two carbon atoms, 3- or 4-membered alkylene having from 3 to 8 carbon atoms, hydroxy-lower alkyl or halo-lower alkyl, lower alkoxy, lower alkylthio, lower alkanesulphinyl, lower alkanesulphonyl, hydroxy, lower alkanoyloxy, lower alkanoyl, halogen and nitro.

Correspondingly esterified carboxy is, for example, lower alkoxycarbonyl, hydroxy-lower alkoxycarbonyl, lower alkoxy-lower alkoxycarbonyl, lower alkanoyloxy-lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl or phenoxycarbonyl.

Amidated carboxy contains as amino group, for example, a free, mono- or di-substituted amino group. The mono-substituted amino group is mono-substituted, for example, by lower alkyl, by phenyl-lower alkyl that is unsubstituted or substituted in the phenyl moiety, or by unsubstituted or substituted phenyl. Di-substituted amino is di-substituted, for example, by lower alkyl, by phenyl-lower alkyl that is unsubstituted or substituted in the phenyl moiety, and/or by substituted or unsubstituted phenyl or by lower alkylene or lower alkenylene respectively or lower alkylene or lower alkenylene respectively each interrupted by monoaza, N-alkylated monoaza, monoxa or monothia, lower alkylene or lower alkenylene having one or two ortho-fused benzo systems and/or being branched or unbranched. Substituted phenyl is, for example, mono- or poly-substituted, for example by an aliphatic radical, such as lower alkyl, lower

B11

alkenyl, optionally branched, especially bridging two carbon atoms, 3- or 4-membered alkylene having from 3 to 8 carbon atoms, hydroxy-lower alkyl or halo-lower alkyl, lower alkoxy, lower alkylthio, lower alkanesulphinyl, lower alkanesulphonyl, hydroxy, lower alkanoyloxy, lower alkanoyl, halogen and/or nitro. Correspondingly amidated carboxy is, for example, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, N-mono- and N,N-diphenyl-lower alkylcarbamoyl, N-mono- or N,N-diphenylcarbamoyl, lower alkylenecarbamoyl or lower alkylenecarbamoyl interrupted by monoaza, N'-lower alkylmonoaza, monooxa or monothia, and also N-lower alkyl-N-phenyl-lower alkyl-, N-phenyl-lower alkyl-N-phenyl- and lower alkenyl-carbamoyl.

The aromatic ring A may be additionally mono- or poly-substituted by an aliphatic radical, such as lower alkyl, hydroxy-lower alkyl, halo-lower alkyl, lower alkenyl, or optionally branched, especially bridging two adjacent carbon atoms, 3- or 4-membered alkylene, lower alkoxy, hydroxy, lower alkylthio, lower alkanesulphinyl, lower alkanesulphonyl, halogen, lower alkanoyloxy, lower alkanoyl and/or nitro, or, except for R_3, it may be unsubstituted.

An amino group di-substituted by two monovalent hydrocarbon radicals contains, as such radicals, monovalent aliphatic radicals, such as lower alkyl radicals, which may be unsubstituted or substituted by 3-to 7-membered cycloalkyl or by aryl, such as phenyl that is unsubstituted or substituted by an aliphatic radical, such as lower alkyl, lower alkenyl, lower alkylene, hydroxy-lower alkyl, halo-lower alkyl, lower alkoxy, lower alkylthio, lower alkanesulphinyl, lower alkanesulphonyl, hydroxy, halogen, lower alkanoyloxy, lower alkanoyl and/or nitro. An amino group di-substituted by a divalent hydrocarbon radical contains as that radical a divalent aliphatic radical, which may also be interrupted by aza, N-lower alkylaza, oxa or thia, such as lower alkylene, lower alkenylene, or lower alkylene or lower alkanylene each interrupted by aza, N-lower alkylaza, oxa or thia; lower alkylene and lower alkenylene may also be branched. Such cyclic amines R_3 may also have one or two ortho-fused benzo systems.

R_3 preferably represents di-lower alkylamino, cycloalkyl-lower alkyl-lower alkylamino, dicycloalkyl-lower alkylamino, lower alkylphenyl-lower alkylamino, diphenyl-lower alkylamino, also phenyl-lower alkyl-cyclo-lower alkyl-lower alkylamino, and also in each case 5- to 8-membered lower alkyleneamino, lower alkenyleneamino, aza-lower alkyleneamino, N'-lower alkylaza-lower alkyleneamino, oxa-lower alkyleneamino, thia-lower alkyleneamino, aza-lower alkenyleneamino, N'-lower alkylaza-lower alkenyleneamino, oxa-lower alkenyleneamino or thia-lower alkenyleneamino; lower alkyleneamino and lower alkenyleneamino may also be branched and accordingly may have from 4 to 14, preferably from 4 to 7, carbon atoms.

There may be mentioned as examples of such radicals R_3: pyrrolidin-1-yl, 2- or 3-pyrrolin-1-yl, pyrrol-1-yl, piperidin-1-yl, azepin-1-yl, imidazolidin-1-yl, 2-, 3- or 4-imidazolin-1-yl, oxazolidin-3-yl, 4-oxazolin-3-yl, thiazolidin-3-yl, 4-thiazolin-3-yl, piperazin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, 3-methylimidazolidin-1-yl and 4-methylpiperazin-1-yl.

R_3 also represents lower alkylene- or lower alkenylene-amino having one or two ortho-fused benzo systems, such as indol-1-yl, indolin-1-yl, isoindol-2-yl, isoindolin-2-yl, carbazol-9-yl or β-carbolin-9-yl.

Hereinbefore and hereinafter, organic radicals and compounds designated "lower" should preferably be understood as being those that contain up to and including 7, especially up to and including 4, carbon atoms.

The general definitions used within the framework of the present text have, especially, the following meanings:

Lower alkyl is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl and also includes, correspondingly, pentyl, hexyl and heptyl radicals.

Hydroxy-lower alkyl is, for example, hydroxymethyl, 2-hydroxyethyl or 2- or 3-hydroxypropyl.

Halo-lower alkyl is, for example, chloromethyl or trifluoromethyl.

Lower alkenyl is, for example, vinyl, 1- or 2-propyenyl, 1-, 2- or 3-butenyl or butadien-1,3-yl.

3- or 4-membered alkylene is, for example, straight-chained, such as tri- or tetra-methylene, or branched, such as 2,4-butylene, 2,4-pentylene or 2-methyl-1,3-propylene.

Lower alkoxy is, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.-butoxy, tert.-butoxy and also includes, correspondingly, pentyloxy, hexyloxy and heptyloxy radicals.

Lower alkythio is, for example, methyl-, ethyl-, n-propyl-, isopropyl-, n-butyl-, isobutyl-, sec.-butyl- or tert.-butyl-thio.

Lower alkane-sulphinyl or -sulphonyl is, for example, methane-, ethane-, n-propane- or isopropane-sulphinyl or -sulphonyl.

Halogen is, for example, halogen having an atomic number of up to and including 53, such as fluorine, chlorine or bromine, and also includes iodine.

Lower alkanoyloxy is, for example, acetoxy, propionyloxy, butyryloxy, isobutyryloxy, sec.- or tert.- butyryloxy.

Lower alkanoyl is, for example, acetyl, propionyl, butyryl, isobutyryl or tert.-butyryl.

3- to 7-membered cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

Lower alkylene is, for example, straight-chained, such as 4- to 7-membered lower alkylene, such as tetra-, penta- or hexa-methylene, and also heptamethylene, or branched, such as 2,3-dimethyl- or 2,3-diethyl-1,4-butylene.

Lower alkylene interrupted by aza or N-lower alkylaza is, for example, 4- to 7-membered monoaza- or N'-lower alkylmonoaza-lower alkylene, such as 2-azatetra-methylene, 3-azapentamethylene or 3-methylazapentamethylene.

Lower alkylene interrupted by oxa or thia is, for example, monooxa- or monothia-lower alkylene, such as 3-oxa or 3-thia-pentamethylene.

Lower alkenylene has one or more double bonds and is, for example, 4- to 7-membered lower alkenylene, such as but-2-en-1,4-ylene, buta-1,3-dien-1,4-ylene, pent-2-en-1,5-ylene, or penta-1,3-dien-1,5-ylene, penta-1,4-dien-1,5-ylene, hex-3-en-2,5-ylene or haxa-2,4-dien-2,4-ylene.

Lower alkenylene that has one or more double bonds and that is interrupted by aza or N-lower alkylaza is, for example, 2-azabuten-1-ylene, 2-azabuten-2-ylene, 2-azabuten-3-ylene, 2-methylazabuten-3-ylene or 2-azabutadien-1,3-ylene.

Salts of compounds of the formula (I) according to the invention are preferably pharmaceutically acceptable salts, such as pharmaceutically acceptable acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulphuric acid, phosphoric acid or hydrohalic acids, with strong organic carboxylic acids, such as lower alkenecarboxylic acids, for example glacial acetic acid, optionally unsaturated dicarboxylic acids, for example oxalic, malonic, maleic or fumaric acid, or hydroxycarboxylic acids, for example tartaric acid or citric acid, or with sulphonic acids, such as lower alkane-sulphonic or optionally substituted benzenesulphonic acids, for example methane- or *p*-toluenesulphonic acid. If R_1 is, for example, carboxy, corresponding compounds can form salts with bases. Suitable salts with bases are, for example, corresponding alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, pharmaceutically acceptable transition metal salts,such as zinc or copper salts, or salts with ammonia or organic amines, such as cyclic amines, such as mono-, di- or tri-lower alkylamines, such as hydroxy-lower alkylamines, for example mono-, di-or tri-hydroxy-lower alkylamines, hydroxy-lower alkyl-lower alkylamines or such as polyhydroxy-lower alkylamines. Cyclic amines are, for example, morpholine, thiomorpholine, piperidine or pyrrolidine. There come into consideration as mono-lower alkylamines, for example ethylamine or tert.-butylamine, as di-lower alkylamines, for example diethylamine or diisopropylamine, and as tri-lower alkylamines, for example trimethylamine or triethylamine. Corresponding hydroxy-lower alkylamines are, for example, mono-, di- or tri-ethanolamines, and hydroxy-lower alkyl-lower alkylamines are, for example, N,N-dimethylamino- or N,N-diethylamino-ethanol, and also as polyhydroxy-lower alkylamine glucosamine.

Isomeric compounds of the formula (I) are especially in the form of structural isomers. If, for example, compounds of the formula (I) have chiral carbon atoms, they may be in the form of diastereoisomers, diastereoisomeric mixtures, or racemates or in the form of a pure enantiomer.

The compounds of the formula (I) have valuable pharmacological properties. They have, especially, a pronounced anti-inflammatory action which can be demonstrated, for example, by inhibition of the carrageenin-induced paw oedema in rats at a dose of approximately 0.1 mg/kg p.o. and above analogously to the method described by Pasquale *et al.*, Ag. and Actions, *5*, 256 (1975), and in the adjuvant-arthritis model in rats at a dose of approximately 1.0 mg/kg p.o. and above analogously to the method described by L. Riesterer *et al.*, Pharmacology, *2*, 288 (1969). In addition, compounds of the formula (I) inhibit, *in vitro*, at a concentration of approximately 10 μmol/l and above prostaglandin synthesis from arachidonic acid analogously to the method described by H.L. White *et al.*, Prostaglandins, *7*, 123 (1974).

The compounds of the formula (I) also have a distinct antinociceptive activity that can be demonstrated, for example, by the reduction, described by L. C. Hendershot *et al.*, J. Pharmacol. exp. Therap., *125*, 237 (1959), of the phenyl- *p*-benzoquinone-induced writhing syndrome in mice at a dose of approximately 0.1 mg/kg p.o. and above.

Furthermore, the compounds of the formula (I) have the ability to absorb from the range of the UV spectrum the rays producing erythema on the epidermis (between 290 and 320 nm) while the tanning rays of from approximately 320 to approximately 400 nm are transmitted by the compounds.

Consequently, these compounds can be used as anti-inflammatory agents, (peripheral) analgesics and/or light-screening agent, for example for cosmetic purposes.

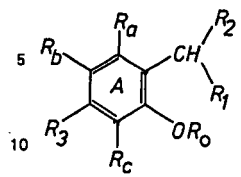
The invention relates, for example, to compounds of the formula (I) in which R_6 represents hydrogen, a lower alkanoyl radical or an aryl-lower alkanoyl radical, R_1 represents carboxy, carboxy esterified by an aliphatic or aromatic alcohol, carbamoyl or mono- or disubstituted carbamoyl, R_2 represents a saturated and unsubstituted aliphatic radical, R_3 represents an amino group di-substituted by two monovalent aliphatic radicals or an amino group di-substituted by a divalent aliphatic radical, and the aromatic ring A may be additionally mono- or poly-substituted by an aliphatic radical, lower alkoxy, lower alkylthio, lower alkanesulphinyl lower alkanesulphonyl, hydroxy, halogen, lower alkanoyloxy, lower alkanoyl and/or nitro or, except for R_3, it may

be unsubstituted, and to their salts, especially pharmaceutically acceptable salts, and isomers.

The invention relates, for example, to compounds of the formula (I) in which R_0 represents hydrogen, lower alkanoyl or phenyl-lower alkanoyl in which the phenyl radical may be unsubstituted or mono- or poly-substituted by lower alkyl, hydroxy-lower alkyl, halo-lower alkyl, lower alkenyl, 3- or 4-membered alkylene, lower alkoxy, lower alkylthio, lower alkensulphinyl, lower alkanesulphonyl, hydroxy, halogen, lower alkanoyloxy, lower alkanoyl and/or nitro, or phenyl-lower alkanoyl deriving from a phenyl-lower alkanecarboxylic acid of the formula (I) in which R_0 is hydrogen or lower alkanoyl and R_2 and R_3 as well as the substituents of the ring A have the meanings given below, R_1 represents carboxy, lower alkoxycarbonyl, hydroxy-lower alkoxycarbonyl, lower alkanoyloxy-lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl, phenoxy-carbonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, N-mono- or N,N-di-phenyl-lower alkylcarbamoyl, N-mono- or N,N-di-phenylcarbamoyl, N-lower alkyl-N-phenyl-lower alkyl-carbamoyl, N-lower alkyl-N-phenylcarbamoyl, N-phenyl-lower alkyl-N-phenylcarbamoyl, lower alkylene-carbamoyl, or lower alkylenecarbamoyl or lower alkenylenecarbamoyl each interrupted by monoaza, N'-lower alkylmonoaza, monooxa or monothia, wherein phenyl and phenoxy may in each case be unsubstituted or mono- or poly-substituted by lower alkyl, hydroxy-lower alkyl, halo-lower alkyl, lower alkenyl, 3- or 4-membered alkylene, lower alkoxy, lower alkythio, lower alkanesulphinyl, lower alkane-sulphonyl, hydroxy, halogen, lower alkanoyloxy, lower alkanoyl and/or nitro, lower alkylene or lower alkenylene having one or two ortho-fused benzo systems and/or being branched or unbranched, R_2 represents hydrogen or lower alkyl and R_3 represents, on the one hand, N,N-di-lower alkylamino, N-cyclo-lower alkyl-N-lower alkylamino, N-lower alkyl-N-phenyl-lower alkylamino, N,N-dicyclo-lower alkyl-lower alkylamino, N-cyclo-lower alkyl-lower alkyl-N-phenyl-lower alkylamino or N,N-diphenyl-lower alkylamino or, on the other hand, in each case 5- to 8-membered lower alkyleneamino, lower alkenyleneamino, lower alkyleneamino interrupted by monoaza, N'-lower alkylmonoaza, monooxa or monothia, lower alkenyleneamino interrupted by monoaza, N'-lower alkylmonoaza, monooxa or monothia, or lower alkyleneamino or lower alkenyleneamino containing one or two ortho-fused benzo systems, wherein lower alkylene and lower alkenylene may also be branched and may contain from 4 to 14, especially from 4 to 7, carbon atoms, and/or having one or two ortho-fused benzo systems, and phenyl or benzo may each be unsubstituted or mono- or poly-substituted by lower alkyl, hydroxy-lower alkyl, halo-lower alkyl, lower alkenyl, 3- or 4-membered alkylene, lower alkoxy, lower alkylthio, lower alkenesulphinyl, lower alkanesulphonyl, hydroxy, halogen, lower alkanoyloxy, lower alkanoyl and/or nitro, and the aromatic ring A may be mono- or poly-substituted by lower alkyl, hydroxy-lower alkyl, halo-lower alkyl, lower alkenyl, 3- or 4-membered alkylene, lower alkoxy, lower alkylthio, lower alkeanesulphinyl, lower alkanesulphonyl, hydroxy, halogen, lower alkanoyloxy, lower alkanoyl and/or nitro or, except for R_3, it may be unsubstituted, and to their salts, especially pharmaceutically acceptable salts, and isomers.

The invention relates, for example, to compounds of the formula (I) in which R_0 represents hydrogen, lower alkanoyloxy or phenyl-lower alkanoyloxy the phenyl moiety of which is unsubstituted or mono- or poly-substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy and/or trifluoromethyl, R_1 represents carboxy; carboxy esterified by a lower alkanol, by a lower alkanol substituted by hydroxy, lower alkoxy, lower alkanoyloxy or phenyl the phenyl moiety of which is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy and/or trifluoromethyl, or by a phenol that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy and/or trifluoromethyl; carbamoyl; carbamoyl that is mono-substituted by lower alkyl, or by phenyl-lower alkyl the phenyl moiety of which is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy and/or trifluoromethyl; or carbamoyl that is di-substituted by lower alkyl, by phenyl-lower alkyl the phenyl moiety of which is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy and/or trifluoromethyl, by lower alkylene, or by lower alkylene that is interrupted by monoaza, N-alkylated monoaza, monooxa or monothia, R_2 represents hydrogen or lower alkyl, R_3 represents an amino group di-substituted by lower alkyl, by 3 to 7-membered cycloalkyl-lower alkyl, by phenyl-lower alkyl the phenyl moiety of which is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy and/or trifluoromethyl, by lower alkylene, by lower alkenylene, by lower alkylene interrupted by aza, N-lower alkylaza, oxa or thia, or by lower alkenylene interrupted by aza or N-lower alkylaza, and the aromatic ring A may be additionally substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy, 3- or 4-membered alkylene and/or trifluoromethyl, and to their salts, especially pharmaceutically acceptable salts, and isomers.

The invention relates especially to compounds of the formula



(Ia),

in which R_0 represents hydrogen or lower alkanoyl, such as acetyl, R_1 represents carboxy, lower alkoxycarbonyl, such as methoxycarbonyl, lower alkylenecarbamoyl, such as pyrrolidinocarbonyl, or oxa-lower alkylene-carbamoyl, such as 3-oxapentamethylenecarbamoyl, R_2 represents hydrogen or lower alkyl, such as methyl, R_3 represents di-lower alkylamino, such as dimethylamino, dicyclo-alkyl-lower alkylamino, such as dicyclopropylmethylamino, diphenyl-lower alkylamino, such as dibenzylamino, 5- to 8-membered lower alkyleneamino, such as pyrrolidin-1-yl, 5- to 8-membered lower alkenyleneamino, such as pyrrol-1-yl, 5- to 8-membered monoaza-lower alkyleneamino, such as piperazin-1-yl, 5- to 8-membered N'-lower alkylmonoaza-lower alkyleneamino, such as 4-methylpiperazin-1-yl, 5- to 8-membered monoaza-lower alkyleneamino, such as morpholin-4-yl, 5- to 8-membered monothia-lower alkyleneamino, such as thiomorpholin-4-yl, 5- to 8-membered monoaza-lower alkenyleneamino, such as imidazol-1-yl, or 5- to 8-membered N'-lower alkylmonoaza-lower alkenyleneamino, such as 3-methyl-imidazol-1-yl, and each of R_a, R_b and R_c, independently of one another, represents hydrogen, lower alkyl, such as methyl, lower alkoxy, such as methoxy, hydroxy, halogen, such as chlorine, lower alkanoyloxy, such as acetoxy, 3- or 4-membered alkylene, such as tetramethylene, or trifluoromethyl, and to their salts, especially pharmaceutically acceptable salts, and isomers.

The invention relates especially to compounds of the formula (Ia) in which R_0 represents hydrogen or lower alkanoyl, such as acetyl, or phenyl-lower alkanoyl deriving from a phenyl-lower alkanecarboxylic acid of the formula (I), in which R_0 is hydrogen and R_2, R_3, R_a, R_b and R_c have the meanings given below, R_1 represents carboxy, lower alkoxycarbonyl, such as methoxycarbonyl, lower alkanoyloxy-lower alkoxycarbonyl, such as pivaloyloxy-methoxycarbonyl, N,N-diphenyl-lower alkylcarbamoyl, such as N,N-dibenzylcarbamoyl, lower alkylene-carbamoyl, such as pyrrolidinocarbonyl, or lower alkylenecarbamoyl interrupted by monooxa, such as 4-morpholinocarbonyl, R_2 represents hydrogen or lower alkyl, such as methyl, R_3 represents, on the one hand, N,N-diphenyl-lower alkylamino, such as dibenzylamino, or, on the other hand, 5- to 8-membered lower alkyleneamino, such as 1-piperidino, 5- or 8-membered lower alkenyleneamino, such as pyrrol-1-yl, 5- to 8-membered lower alkyleneamino interrupted by monooxa, such as 4-morpholino, or 5- to 8-membered lower alkyleneamino or lower alkenyleneamino respectively having one ortho-fused benzo system, such as Indolin-1-yl or Indol-1-yl, and/or each of R_a, R_b and R_c, independently of one another, represents hydrogen, lower alkyl, such as methyl, or halogen, such as chlorine or bromine, and to their salts, especially pharmaceutically acceptable salts, and isomers.

The invention relates more especially to compounds of the formula (Ia) in which R_0 represents hydrogen or lower alkanoyl, especially having up to and including 5 carbon atoms, such as acetyl, R_1 represents carboxy, lower alkoxycarbonyl, especially having up to and including 5 carbon atoms, such as methoxycarbonyl, 5- to 8-membered lower alkylenecarbamoyl, such as pyrrolidinocarbonyl, or 5- to 8-membered monooxa-lower alkylene-carbamoyl, such as 3-oxapentamethylenecarbamoyl, R_2 represents hydrogen or lower alkyl, especially having up to and including 4 carbon atoms, such as methyl, R_3 represents di-lower alkylamino, especially having up to and including 4 carbon atoms in the alkyl moiety, such as N,N-dimethylamino, 5- to 8-membered lower alkyleneamino, such as pyrrolidin-1-yl, 5- to 8-membered lower alkenyleneamino, such as pyrrol-1-yl, or 5- to 8-membered monooxa-lower alkyleneamino, such as morpholin-4-yl, each of R_a and R_c represents hydrogen and R_b represents halogen, especially having an atomic number of up to and including 35, such as chlorine, and to their salts, especially pharmaceutically acceptable salts, and isomers.

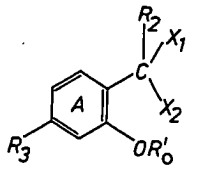
The invention relates above all to compounds of the formula (Ia) in which R_0 represents hydrogen or lower alkanoyl having up to and including 5 carbon atoms, such as acetyl, R_1 represents carboxy or lower alkoxy-carbonyl having up to and including 5 carbon atoms, such as methoxycarbonyl, R_2 represents lower alkyl having up to and including 4 carbon atoms, such as methyl, R_3 represents 5- to 7-membered lower alkylene-amino, such as pyrrolidin-1-yl, morpholin-4-yl or pyrrol-1-yl, each of R_a and R_c represents hydrogen and R_b represents lower alkyl having up to and including 4 carbon atoms, such as methyl, or halogen having an atomic number of up to and including 35, such as chlorine, and to their salts, especially pharmaceuti-

cally acceptable salts, and isomers.

The invention relates above all to compounds of the formula (Ia) in which R_0 represents lower alkanoyl having up to and including 5 carbon atoms, such as acetyl, R_1 represents lower alkoxycarbonyl having up to and including 5 carbon atoms, such as methoxycarbonyl, R_2 represents lower alkyl having up to and including 4 carbon atoms, such as methyl, R_3 represents morpholin-4-yl or pyrrol-1-yl, each of R_4 and R_5 represents hydrogen, and R_6 represents halogen having an atomic number of up to and including 35, such as chlorine, or lower alkyl having up to and including 4 carbon atoms, such as methyl, and to their salts, especially pharmaceutically acceptable salts, and isomers.

The invention relates in particular to the novel compounds mentioned in the Examples, their salts, especially pharmaceutically acceptable salts, and isomers, and also to the processes for the manufacture thereof described in the Examples.

The compounds of the present invention are manufactured in a manner known *per se*, for example by treating with solvolysis agents compounds of the formula



(II),

in which X_1 is hydrogen, X_2 represents functionally modified carboxy that is different from R_1, and R'_0 has the same meaning as R_0, or in which X_1 is hydrogen and X_2 together with R'_0 forms the group

or in which X_1 together with X_2 forms the group $=C=O$ or the group $=C(Hal)_2$, Hal in each case representing halogen, and R'_0 has the same meaning as R_0, or salts thereof and, if desired, converting a salt obtainable according to the process into the free compound or into a different salt, converting a free compound obtainable according to the process into a different free compound or into a salt and/or, if desired, separating an isomeric mixture obtainable according to the process into its components.

Functionally modified carboxy X_2 that is different from R_1 is, for example, cyano, anhydridised carboxy, optionally substituted amidino, optionally esterified thiocarboxy, optionally esterified dithiocarboxy, optionally substituted thiocarbamoyl, optionally esterified or anhydridised carboximidoyl, esterified or amidated carboxy that is different from esterified or amidated carboxy R_1, carbamoyl substituted by hydroxy or amino, trialkoxymethyl or trihalomethyl.

Anhydridised carboxy is, for example, carboxy anhydridised by a mineral acid, such as a hydrohalic acid, or by a carboxylic acid, such as an optionally substituted lower alkanoic or benzoic acid, or a carbonic acid halide lower alkyl semiester. There may be mentioned as examples halocarbonyl, such as chlorocarbonyl, lower alkanoyloxycarbonyl, such as acetoxycarbonyl, or lower alkoxycarbonyloxycarbonyl, such as ethoxycarbonyloxycarbonyl.

Optionally substituted amidino is, for example, amidino substituted by an aliphatic radical, for example a lower alkyl radical, such as amidio or lower alkylamidino, for example ethylamidino.

Optionally esterified thiocarboxy or dithiocarboxy has, for example, the alcohol or hydroxy components mentioned in connection with esterified carboxy. There may be singled out as examples lower alkylthiocarbonyl, such as ethylthiocarbonyl, lower alkoxythiocarbonyl, such as ethoxythiocarbonyl, lower alkylthiothiocarbonyl, such as ethylthiothiocarbonyl, and the respective thiocarboxy and dithiocarboxy.

Optionally substituted thiocarbamoyl may contain, for example, the substituents mentioned under amidated carboxy. There may be mentioned as examples N-mono- or N,N-di-lower alkylthiocarbamoyl, such as methyl- or diethyl-thiocarbamoyl, and also thiocarbamoyl, such as 4-thiomorpholinyl- or 4-morpholinyl-thiocarbonyl.

There are to be understood by alkoxy- and halocarbimidoyl, for example, lower alkoxycarbimidoyl, such as ethoxycarbimidoyl, and chlorocarbimidoyl, respectively.

Trihalomethyl is, for example, trichloromethyl, and trialkoxymethyl is, for example, tri-lower alkoxymethyl, such as trimethoxymethyl.

Solvolysis agents are, for example, water, alcohols corresponding to the desired esterified carboxy group, ammonia, or amines corresponding to the desired amidated carboxy group.

The treatment with a corresponding solvolysis agent is optionally carried out in the presence of an acid or base, optionally while cooling or heating and, for example between −20° and 300°C, if necessary, in an inert solvent or diluent. Besides a solvolysis agent, as solvent can be used, for example, an ether, such as dioxane or tetrahydrofuran, an amide, such as dimethylformamide, or a mixture thereof.

There come into consideration as acids, for example, inorganic or organic protonic acids, such as mineral acids, for example sulphuric acid or a hydrohalic acid, for example hydrochloric acid, sulphonic acids, for example lower alkanesulphonic or optionally substituted benzenesulphonic acid, for example methanesulphonic or *p*-toluenesulophonic acid, or carboxylic acids, for example lower alkanecarboxylic acids, for example acetic acid, whilst, for example, alkali metal hydroxides, for example sodium or potassium hydroxide, may be used as bases.

Compounds of the formula (II) in which X_1 represents hydrogen, X_2 represents functionally modified carboxy that is different from R_1 and R'_0 has the same meaning as R_0, or in which X_1 represents hydrogen and X_2 together with R'_0 forms the group

are converted, for example by solvolysis, into corresponding compounds of the formula (I). In this operation, for example the cyano group, optionally substituted amidino, anhydridised carboxy, optionally esterified thiocarboxy, optionally esterified dithiocarboxy, optionally substituted thiocarbamoyl, optionally esterified or anhydridised carboximidoyl, esterified or amidated carboxy that is different from esterified or amidated caboxy R_1, carbamoyl substituted by hydroxy or amino, tri-lower alkoxymethyl, lower alkoxyhalomethyl or trihalomethyl is hydrolysed to carboxy. Cyano, optionally S-esterified thiocarboxy, anhydridised carboxy, esterified or amidated carboxy that is different from esterified or amidated carboxy R_1, and carbamoyl substituted by hydroxy or amino are, for example, alcoholysed with a suitable alcohol to form esterified carboxy, and cyano and anhydridised carboxy are, for example, ammonolysed or aminolysed with ammonia or a suitable amine to form amidated carboxy. Lower alkanoyloxy radicals or acyloxy radicals $-OR_0$ optionally positioned at the ring A may, for example, be hydrolysed to hydroxy in the course of the hydrolysis.

Lactones of the formula (II), that is to say compounds of the formula (II) in which X_1 represents hydrogen and X_2 together with R'_0 forms the group

are hydrolysed, for example in the presence of an acid or especially a base, to compounds of the formula (I) in which R_1 represents carboxy or carboxylate and R_0 represents hydrogen.

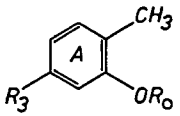
In a preferred embodiment of the above process compounds of the formula (II) in which X_1 represents hydrogen and X_2 together with R'_0 forms the group

are used as starting materials and are reacted with an alkali metal hydroxide while heating, for example at from approximately 0° to approximately 150°C, with hydrolytic cleavage of the lactone ring, to form compounds of the formula (I) or salts thereof in which R_1 represents carboxy or carboxylate and R_0 represents hydrogen. In the subsequent optional reactions, if desired carboxy R_1 is converted into amidated or esterified carboxy R_1 and hydroxy $-OR_0$ is converted into esterified hydroxy-OR_0.

Ketenes of the formula (II), that is to say compounds of the formula (II) in which X_1 and X_2 together form the group $=C=O$ and R'_0 has the same meaning as R_0, may be converted, for example by the addition of water, a suitable alcohol, ammonia or a suitable amine, into corresponding compounds of the formula (I) or salts thereof.

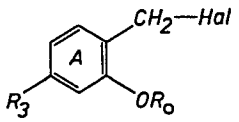
Compounds of the formula (II) in which X_1 and X_2 together form the group $=C(Hal)_2$ and R'_0 has the same meaning as R_0, may be converted, for example by hydrolysis with water, especially in the presence of an acid, such as a mineral acid, for example sulphuric acid, optionally while heating, such as within a temperature of from approximately 50° to approximately 150°C, into compounds of the formula (I) in which R_1 represents carboxy,

The starting materials of the formula (II) or salts thereof in which X_1 represents hydrogen, X_2 represents functionally modified carboxy that is different from R_1 and R'_1 has the same meaning as R_1 are obtained according to known methods. For example, compounds of the formula



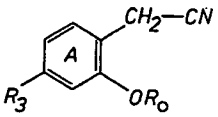
(IIa)

or salts thereof are used as starting materials. These are reacted, for example, with halogenation agents, such as N-bromosuccinimide, in the presence of a radical former, such as benzoyl peroxide or azobisisobutyronitrile, while heating in an inert solvent, such as benzene, to form compounds of the formula



(IIb),

in which Hal represents halogen, especially bromine or chlorine, or salts thereof. The compounds of the formula (IIb) obtainable in this manner are converted into the corresponding nitriles by treatment with alkali metal cyanides, for example sodium cyanide, optionally while heating in a suitable solvent, such as dimethyl sulphoxide. In an optional step, the radical R_2 can be introduced into the resulting compounds of the formula



(IIc)

or salts thereof by reaction with a compound R_2-Hal, in which Hal represents halogen, in the presence of a base, such as an alkali metal amide or hydride, for example sodium amide or hydride, at low temperatures, for example below 10°C, and in a suitable solvent, such as dimethylformamide.

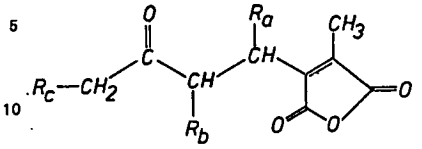
The cyano group can then, if desired, be converted in a manner known *per se* into other functionally modified carboxy groups that are different from R_1, for example into optionally substituted amidino, optionally substituted thiocarbamoyl, optionally esterified or anhydridised carboximidoyl, or amidated or esterified carboxy that is different from amidated or esterified carboxy R_1.

Thus, for example, from the cyano group it is possible to obtain the corresponding alkoxycarbimidoyl, for example by treating with an alcohol in the presence of a strong acid; the carbamoyl by treating with hydrogen peroxide in the presence of a protonic acid; the corresponding thiocarbamoyl by treating with hydrogen sulphide in the presence of an inorganic base; and the corresponding esterified carboxy by reacting with an excess of alcohol in the presence of an acid. In turn, there may be obtained from alkoxycarbimidoyl, for example by treatment with ammonia or a primary or secondary amine, for example corresponding amidino, and by reacting with at least 2 equivalents of an alcohol, for example corresponding trialkoxymethyl.

In a preferred embodiment, lactones of the formula (II) in which X_1 represents hydrogen and X_2 together with R'_1 forms the group

and in which the ring A may be unsubstituted except for R_3, or mono- or poly-substituted by lower alkyl, or optionally additionally di-substituted by 3- or 4-membered alkylene and R_3

represents methyl are obtained by reacting with amines of the formula R_3–H or with acid addition salts thereof compounds of the formula

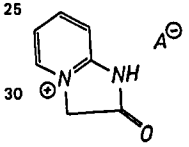


(IId)

in which each of R_a, R_b and R_c independently of one another, represents hydrogen, lower alkyl or 3- or 4-membered alkylene.

The reaction is carried out, for example, at elevated temperature, for example in the melt or at the reflux temperature of the solvent, for example within a temperature range of from approximately 80°C to approximately 200°C. Suitable inert solvents are, for example, higher-boiling hydrocarbons, such as aromatic hydrocarbons, for example benzene, toluene or xylenes. The amines of the formula R_3H are used especially in the form of acid addition salts, for example advantageously in the form of benzoates.

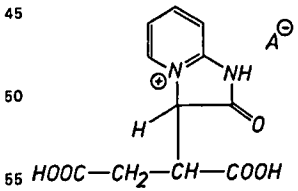
For the manufacture of compounds of the formula (IId) in which R_a represents hydrogen, compounds of the formula



(IIe)

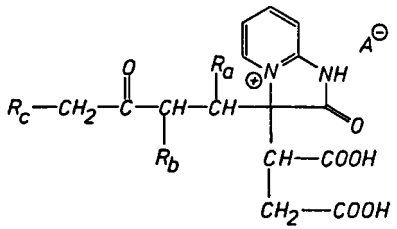
which are optionally substituted in the aromatic moiety and in which $A^{\ominus}$ represents the anion of an inorganic or organic acid, are used as starting materials and are reacted with fumaric acid, maleic acid or maleic acid anhydride in the presence of a base, inorganic or organic bases being suitable. Inorganic bases are, for example, alkali metal hydroxides or hydrides, such as sodium or potassium hydroxide or sodium or potassium hydride. There are used as organic amines, for example, tertiary amines, such as trialkylamines, for example triethylamines or tri-n-butylamines, or cyclic amines, such as pyridine, picoline, quinoline or lutidine.

The free compounds initially obtainable by this method are converted by treatment with organic or inorganic acids into the salts of the formula



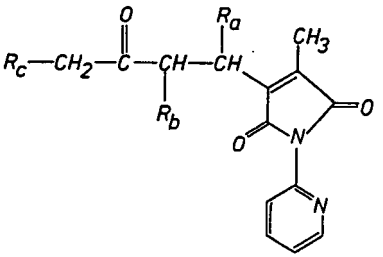
(IIf).

In the further course of the reaction, these compounds are reacted, optionally in the presence of one of the above-mentioned bases, with compounds of the formula R_e–CH = $C(R_d)$–CO–CH_2–R_e (IIg) to form compounds of the formula



(IIh)

which are converted in the next reaction step by heating, for example at temperatures of between 80 and 160°C, with decarboxylation, into compounds of the formula

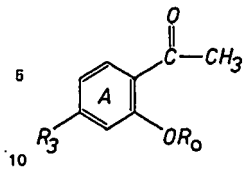


(IIi).

The thermal conversion of compounds of the formula (IIh) into compounds of the formula (IIi) is carried out, for example, in an optionally halogenated aromatic solvent, such as benzene, toluene, a xylene or chlorobenzene, or a lower alkanecarboxylic acid, such as glacial acetic acid. The compounds of the formula (IIi) are then hydrolysed to form compounds of the formula (IId). The hydrolysis is carried out, for example, in aqueous or aqueous-organic medium. Suitable organic solvents are especially high-boiling polar solvents, such as an ether, for example dioxane or tetrahydrofurane, N,N-dialkylamides, for example N,N-dimethylformamide or N,N-dimethylacetamide, or cyclic amides, such as N-methylpyrroldione. The hydrolysis is carried out, for example, with the aid of an inorganic or organic acid, mineral acids, such as hydrohalic acids or sulphuric acid, being suitable as inorganic acids, and sulphonic acids, such as lower alkane- or optionally substituted benzene-sulphonic acids, such as methane- or *p*-toluene-sulphonic acid, or optionally substituted alkanecarboxylic acids, such as glacial acetic acid, being suitable as organic acids.

For the manufacture of compounds of formula (IId) in which R_3 is other than hydrogen, compounds of the formula (IIe) are used as starting materials and are reacted first with compounds of the formula (IIg) and then with fumaric acid, maleic acid or especially with maleic acid anhydride to form compounds of the formula (IIh) which, in turn, as described above, further react to form the corresponding compounds of the formula (IId).

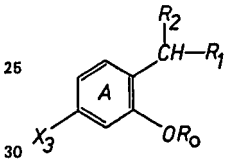
In a further advantageous method of procedure, compounds of the formula (II) in which X_1 represents hydrogen, X_2 represents functionally modified carboxy that is different from R_1 and R_c has the same meaning as R_c, and in which R_2 represents hydrogen, are obtained by using compounds of the formula



(IIk)

or salts thereof as starting materials and reacting these under pressure with sulphur and a primary or secondary amine, advantageously with morpholine or thiomorpholine, or with ammonium polysulphide, analogously to the Willgerodt (-Kindler) reaction. In a compound of the formula (II) obtainable in this manner X_2 represents substituted carbamoyl or correspondingly substituted thiocarbamoyl that is different from R_1, which can be converted in a manner known *per se*, for example by corresponding solvolysis, into other functionally modified carboxy X_2 that is different from R_1.

The novel compounds of the formula (I) can furthermore be manufactured by converting X_3 into R_3 in compounds of the formula



(III)

or salts thereof in which X_3 represents a radical that can be converted into R_3, and, if desired, converting a salt obtainable according to the process into the free compound or into a different salt, converting a free compound obtainable according to the process into a different free compound or into a salt and/or, if desired, separating an isomeric mixture obtainable according to the process into its components.

A radical X_3 that can be converted into R_3 represents, for example, amino or a group of the formula $-NH-A_1-X_4$ or $-NH-A_2-X_5$, in which A_1 represents a divalent hydrocarbon radical, for example optionally branched lower alkylene, X_4 represents hydrogen, 3- to 7-membered cycloalkyl or aryl, such as phenyl that is unsubstituted or substituted by an aliphatic radical, lower alkoxy, lower alkylthio, lower alkanesulphinyl, lower alkanesulphonyl, hydroxy, halogen, lower alkanoyloxy, lower alkanoyl and/or nitro, A_2 represents a divalent hydrocarbon radical, which may also be interrupted by aza, N-lower alkylaza, oxa or thia, for example lower alkylene or lower alkenylene, or lower alkylene interrupted by aza, N-lower alkylaza, oxa or thia, or lower alkenylene interrupted by aza, N-lower alkylaza, oxa or thia, wherein lower alkylene and lower alkenylene may also be branched and furthermore may additionally contain one or two ortho-fused benzo systems, and X_5 represents hydroxy or reactive esterified hydroxy. There is to be understood by reactive esterified hydroxy X_5, for example, hydroxy esterified by a strong inorganic mineral acid, such as a hydrohalic acid or sulphuric acid, by an organic sulphonic acid, such as lower alkanesulphonic or optionally substituted benzenesulphonic acid, for example methanesulphonic or *p*-toluenesulphonic acid, or by an organic carboxylic acid, such as a lower alkanecarboxylic acid, for example acetic acid: for example especially halogen, such as chlorine or bromine, and sulphonyloxy, such as *p*-toluenesulphonyloxy.

The conversion of $-NH-A_1-X_4$ to R_3 is carried out in a manner known *per se*. For example, corresponding compounds of the formula (III) or salt thereof are reacted with compounds of the formula $X_4-A_1-X_5$ (IIIa) or salts thereof. The reaction is carried out optionally in an inert solvent or diluent, under a protective gas, for example nitrogen, and/or, if necessary, in the presence of a condensation agent, such as an alkali metal or alkaline earth metal hydroxide or carbonate or an alkaline earth metal alcoholate, for example sodium hydroxide, potassium bicarbonate or sodium methoxide, for example within a temperature range of from approximately 0° to 150°C. A solvent is, for example, an aliphatic alcohol, such as methanol or ethanol, or an aromatic hydrocarbon.

Th conversion of $-NH-A_2-X_5$ to R_3 is carried out in the afore-described manner.

A radical R_3 representing an amino group di-substituted by a divalent hydrocarbon radical can also be introduced directly, for example by reacting compounds of the formula (III) in which X_3

represents amino, or salts thereof, with compounds of the formula X_3–A_2–X_8 (IIIa'). The reaction is carried out in the aforedescribed manner. In these reactions it is also possible to form *in situ* compounds of the formula (III) in which X_3 represents a group of the formula –NH–A_2–X_8, which further react under the reaction conditions directly to form corresponding compounds of the formula (I).

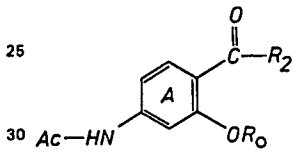
A radical R_3, provided it is of non-aromatic character, may furthermore be introduced directly by using as starting materials, for example, compounds of the formula (III) in which X_3 represents hydrogen, a metal-containing radical or optionally reactive esterified hydroxy, or salts thereof, and reacting these with compounds of the formula R_3–X_8, in which X_8 represents hydrogen, a metal-containing radical or optionally reactive esterified hydroxy, or salts thereof.

A metal-containing radical is, for example, an alkali metal atom, such as lithium or sodium. Reactive esterified hydroxy is, for example, hydroxy esterified by a mineral acid, such as a hydrohalic acid, or a sulphonic acid, such as optionally substituted benzenesulphonic acid.

Especially, for example, compounds of the formula (III) and R_3–X_8 in which one of the radicals X_3 and X_8 is an alkali metal atom, such as lithium, and the other is halogen, such as bromine, are used for the reaction.

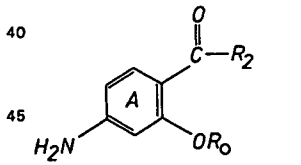
Where X_3 represents hydrogen and X_8 represents hydroxy or halogen, the reaction is carried out in the presence of a Lewis acid. If X_3 represents halogen and X_8 represents hydrogen, the reaction is carried out in the presence of a condensation agent.

For the manufacture of starting materials of the formula (III), the method used is known *per se* and comprises removing the acyl radical, for example from compounds of the formula



(IIIc)

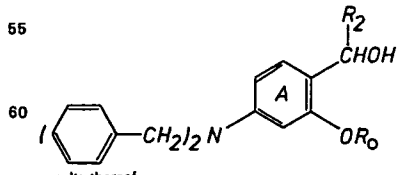
or salts thereof in which Ac represents an acyl radical, such as lower alkanoyl, for example acetyl, in the presence of a base, such as an alkali metal hydroxide, for example sodium hydroxide. In the course of this operation, lower alkanoyloxy groups may be hydrolysed to hydroxy, which can, of course, if desired be esterified again in customary manner. In resulting compounds of the formula



(IIId)

or salts thereof, the amino group is benzylated by reaction with benzyl halides, especially benzyl chloride. This is followed by a reduction of the carbonyl function, for example by means of optionally complex hydrides, for example sodium borohydride.

This reduction yields compounds of the formula



(IIIe)

or salts thereof.

These are reacted, for example, with alkali metal cyanides, such as sodium cyanide, while

heating, and the cyano group is subsequently solvolysed to R_1. In the next reaction step, the benzyl groups are removed by hydrogenolysis in the presence of a hydrogenation catalyst, such as platinum, and the then free amino group is converted by treatment with compounds of the formula X_3–X_8 (IIIf) in the presence of a condensation agent, such as an alkali metal hydroxide, into the radical X_3, wherein X_3 is other than hydrogen, a metal-containing radical or optionally reactive esterified hydroxy.

Compounds of the formula (I), in which R_3 denotes pyrool-1-yl are obtainable by reaction of compounds of the formula (III), in which X_3 is amino, or a salt thereof with 2-buten-1,4-diol or a reactive esterified derivative thereof in the presence of a protonic acid, such as a lower alkanecarboxylic acid, to form the pyrrolin-1-yl substituent an dehydrogenating pyrrolin-1-yl in the presence of a dehydrogenating agent, for example, a quinoline, such as 2,3-dichloro-5,6-dicyano-p-benzoquinone or tetrachloro-p-benzoquinone, or a selenium derivative, such as selenium dioxide, or an element of the subgroup VIII, such as palladium, or by reacting of compounds of the formula (I) in which X_3 is amino or a salt thereof with 2,5-di-lower-alkoxy-tetrahydrofuran, such as 2,5-dimethoxytetrahydrofuran, for example while warming.

Furthermore, the pyrrole ring R_3 can be synthesised by, for example, reacting the amino group X_3 in compounds of the formula (III) with an optionally reactively esterified derivative of 1,3-butadiene-1,4-diol, for example with 1,4-dibromo-1,3-butadiene, if necessary while heating and under a protective gas, for example nitrogen, and in an inert solvent or diluent.

The pyrrole ring R_3 can also be synthesised analogously to the method described by Knorr-Paal by treating the amino group X_3 in compounds of the formula (III) with 1,4-dioxobutane optionally acetalised, it being possible to carry out the reaction under inert conditions, for example under a protective gas while heating and in an inert solvent.

A further process variant for synthesising the pyrrole ring R_3 comprises, for example, reacting compounds of the formula (III) in which X_3 represents, for example, the group of the formula –NH–CH = CH–CH = CH–OH or a reactive esterified form thereof, furthermore a tautomeric form thereof which may be acetalised optionally. In this case the reaction is advantageously carried out under inert conditions and while heating.

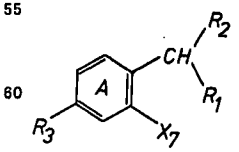
In this context, reactive esterified hydroxy is in each case hydroxy esterified, for example, by a mineral acid, such as a hydrohalic acid, for example hydrobromic acid, or by a sulphonic acid, such as lower alkanesulphonic or optionally substituted benzene-sulphonic acid or p-toluenesulphonic acid.

It is also possible for sufficiently nucleophilic amines R_3–H to be introduced directly into compounds of the formula (III) in which X_3 represents a radical that can be replaced by R_3. If, for example, X_3 represents halogen, especially chlorine, bromine or iodine, the reaction can be carried out in the presence or absence of a solvent and, depending on the choice of halogen atom, at low temperatures up to the boiling temperature of the solvent in question. Advantageously, there is positioned adjacent to X_3 a substituent with a strong $-I$ or $-M$ effect, such as nitro, halogen or trifluoromethyl. In some cases it is of advantage to carry out the reaction under pressure or at elevated temperature. Advantageously the amines are used in excess.

It is also possible for sufficiently nucleophilic amines R_3–H to be introduced directly into compounds of the formula (III) in which each of R_8 and X_3 represents hydrogen. For this purpose, for example corresponding compounds of the formula (III) are first of all treated with an oxidising agent, such as lead-(IV) acetate, for example in the presence of a suitable acid, such as glacial acetic acid, and at room temperature, and then reacted with corresponding amines of the formula R_3–H in an inert solvent, such as an ether, for example dioxan, while heating, for example at reflux temperature, from which there may be obtained especially compounds of the formula (I) in which R_1 represents correspondingly amidated carboxy.

If these reactions are carried out in the presence of a base, any acyl present, such as lower alkanoyloxy, can optionally be hydrolysed to hydroxy and/or esterified or amidated carboxy can optionally be hydrolysed to carboxy.

In a further method, compounds of the formula I in which R_8 represents hydrogen are obtained by converting the radical X_7 into the group $-OR_8$ in compounds of the formula



(IV)

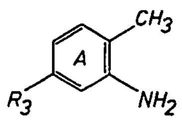
in which X_7 represents a radical that can be converted into the group $-OR_8$, and, if desired,

converting a salt obtainable according to the process into the free compound or into a different salt, converting a free compound obtainable according to the process into a different free compound or into a salt and/or, if desired, separating an isomeric mixture obtainable according to the proces into its components.

A radical X_7 that can be converted into the group $-OR_6$ is, for example, a diazonium group with an anion of an inorganic or organic acid as counterion.

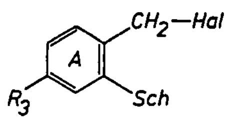
The substitution of the diazonium group by hydroxy is carried out in a manner known *per se*, for example by heating, for example at from approximately 100° to approximately 250°C, in aqueous solution. Frequently, this reaction is carried out in the presence of acids, such as mineral acids, especially sulphuric or orthophosphoric acid, and the hydrogen sulphate ion is preferred as counterion. To avoid azo coupling, the phenol formed is continuously removed from the reaction mixture, for example by extraction by shaking with a suitable solvent.

The starting materials of the formula (IV) can be manufactured in a manner known *per se*, for example by using compounds of the formula



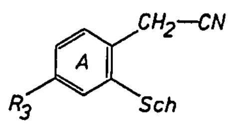
(IVa)

or salts thereof as starting materials and optionally protecting the amino group by introducing a protecting group. There come into consideration as protecting groups, for example acyl or benzyl groups. Advantageously the amino group is benzylated, for example with benzyl chloride. The halogenation of the methyl group which follows, for example bromination with N-bromosuccinimide in the presence of azobisisobutyronitrile while heating, results in the corresponding compounds of the formula



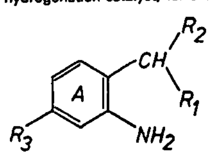
(IVb)

in which Hal represents halogen, especially bromine or chlorine, and Sch represents an optionally protected amino group. These compounds are then reacted with an alkali metal cyanide, such as sodium cyanide, for example while heating in dimethylformamide. If desired, the radical R_2 is introduced into the resulting compounds of the formula



(IVc)

for example by reaction with compounds of the formula R_2-Hal (IVd) in the presence of a base, such as an alkali metal hydride. In the next reaction step, the cyano group is converted into R_1 by customary solvolysis and then the amino-protecting group is removed. Advantageously, the benzyl groups protecting the amino groups are removed by hydrogenolysis in the presence of a hydrogenation catalyst, for example palladium. The resulting compounds of the formula



(IVe)

or salts thereof are treated, for example at low temperatures, with a mineral acid, such as sulphuric acid, and aqueous alkali metal nitrite solution, such as sodium nirtrite solution. The compounds of the formula (IV) formed as intermediates, in which X_7 represents a diazonium group with a corresponding counterion, are further reacted as described above to form compounds of the formula (I).

A radical X_7 that can be converted into the group OR_6 can furthermore represent, for example, etherified hydroxy, or acyloxy that is different from OR_6.

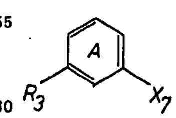
Etherified hydroxy is, for example, hydroxy etherified by an aliphatic alcohol, there coming into consideration as aliphatic alcohol, for example, an optionally substituted alkanol, such as lower alkanol. Examples of such ethers are alkoxy, such as corresponding lower alkoxy, optionally substituted by hydroxy, halogen, alkoxy, for example lower alkoxy, carboxy or a functional derivative thereof, or by nitro, optionally substituted amino, aryl, such as optionally substituted phenyl, alkylthio, alkanesulphinyl, alkane-sulphonyl, or by alkanoyl.

Etherified hydroxy may be converted into hydroxy OR_6, for example, in customary manner by cleaving the ether grouping, for example by treating with a strong protonic acid, such as a hydrohalic acid, for example hydrobromic or hydriodic acid, or with a suitable Lewis acid, such as a halide of elements of main group III, for example boron tribromide. Cleaving the ether grouping with a protonic acid is advantageously carried out at elevated temperature, for example at from approximately 150° to 250°C, and cleaving with a Lewis acid is advantageously carried out while cooling, for example at from approximately −78° to 0°C, or also at room temperature. Furthermore, corresponding ethers can also be cleaved by means of strongly nucleophilic reagents, such as alkali metal lower alkoxides, for example sodium methoxide, strong amides, for example methylamine or triethylamine, or a thiophenolate, for example sodium-*p*-methylthiophenolate, the reaction advantageously being carried out at elevated temperature. The ether cleaving can be carried out, for example, in the presence or absence of a solvent and at temperatures of from approximately 0° to approximately 250°C. There come into consideration as solvent, for example, halogenated hydrocarbons, such as corresponding halo-lower alkanes, for example methylene chloride.

Acyloxy X_7 that is different from acyloxy OR_6 is, for example, aroyloxy, such as optionally substituted alkanoyloxy, there coming into consideration as substituents of aroyloxy, for example benzoyloxy, for example the substituents mentioned at the beginning for phenyl radicals, and as substituents of alkanoyloxy, such as lower alkanoyloxy, for example hydroxy, halogen, alkoxy, carboxy or functional derivatives thereof, nitro, optionally substituted amino, aryl, such as optionally substituted phenyl, alkylthio, alkanesulphinyl, alkanesulphonyl or alkanoyloxy.

Corresponding acyloxy X_7 is converted into hydroxy OR_6 in a manner known *per se*, for example by hydrolysis. The hydrolysis is thus carried out, for example, in the presence of a protonic acid, such as a mineral acid, or advantageously in the presence of a base, such as an alkali metal hydroxide or carbonate, optionally while heating and, for example, in an inert solvent or diluent. In this process functionally modified carboxy R_1 can also be hydrolysed to carboxy. The hydrolysis of the ester OR_1' to OH can be carried out, for example, in an inert solvent, such as a lower alkanol, an ether, for example dioxan, water, an amide, such as dimethylformamide, and mixtures thereof and in a temperature range of from approximately −20° to approximately 300°C. Under these hydrolysis conditions it is also possible for R_1 that is other than carboxy to be hydrolysed.

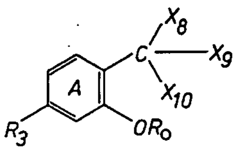
The starting material of the formula (IV) in which X_7 represents etherified acyloxy or acyloxy that is different from OR_6 can, if not known, be manufactured according to processes known *per se*. There is thus used as a starting material, for example, a corresponding 3-nitrophenol and the phenolic OH group is etherified, for example by means of a corresponding alcohol in the presence of a strong mineral acid and while heating, or esterified, for example by means of a corresponding acyl halide. Subsequent reduction of the nitro group, for example by means of hydrogen in the presence of a hydrogenation catalyst, results in the corresponding amine, which can be converted into R_3 analaogously to the manner described above. The resulting compounds of the formula



are acylated, for example with an oxalyl halide derivative, in the presence of a Lewis acid, such as aluminium chloride, and the resulting glyoxylic acid derivative is boiled analogously to the Wolff-Kishner reaction or to the method described by Huang-Minlon, for example with hydrazine in a high-boiling solvent in the presence of a base, such as sodium hydroxide, and the

hydrazone formed as intermediate is thermally decomposed, the carbonyl group being reduced to the methyl group. Subsequently, the radical R_2 may optionally be introduced by reaction with a halide R_2-Hal in the presence of a base, such as sodium amide.

The compounds according to the invention can furthermore be manufactured by converting by reduction into the corresponding compounds of the formula (I) compounds of the formula



(V)

or salts thereof in which each of X_8 and X_9 represents carboxy and X_{10} has the same meaning as R_2; in which X_8 has the same meaning as R_1, X_9 has the same meaning as R_2 and X_{10} represents hydroxy, functionally modified hydroxy, mercapto substituted by a hydrocarbon radical or secondary amino; in which X_8 has the same meaning as R_1 and X_9 and X_{10} together represent oxo, thioxo or optionally substituted hydrazonon, or in which X has the same meaning as R_1 and X_9 and X_{10} together form the group $= R_2'$ or a tautomeric form thereof, and R_2' represents a divalent aliphatic radical, and, if desired, converting a salt obtainable according to the process into the free compound or into a different salt, converting a free compound obtainable according to the process into a different free compound or into a salt and/or, if desired, separating an isomeric mixture obtainable according to the process into its components.

Functionally modified hydroxy is, for example etherified hydroxy, such as hydroxy etherified by a lower alkanol, for example methanol, or reactive esterified hydroxy, for example hydroxy esterified by strong mineral acids, by organic sulphonic acids, such as lower alkanesulphonic or optionally substituted benzenesulphonic acid, or by organic carboxylic acids, such as lower alkanecarboxylic acid.

Secondary amino is, for example, dialkylamino, such as di-lower alkylamino, or diphenylsulphamoyl optionally substituted in the phenyl moiety, especially di(*p*-toluene)-sulphamoyl or di-(*p*-bromophenyl)-sulphamoyl.

Mercapto substituted by a hydrocarbon radical represents, for example, mercapto substituted by an alkyl radical, and the alkyl radical may in turn optionally be substituted for example by an aromatic, such as optionally substituted phenyl, radical, such as lower alkylthio, for example methyl- or ethyl-thio, or phenyl-lower alkythio, for example benzylthio.

Hydrazono may be substituted, for example, by a sulphonyl radical, such as optionally substituted phenylsulphonyl, for example *p*-toluenesulphonyl, or by an optionally substituted phenyl radical.

A divalent aliphatic radical is, for example, a lower alkylidene or lower alkenylidene radical and there comes into consideration as the tautomeric form of $= R_2'$, for example, a corresponding lower alkenylene radical having one or more double bonds.

The reduction is carried out in a manner known *per se*, for example under inert conditions, such as under a protective gas, for example nitrogen, in an inert solvent or diluent, optionally under pressure and/or while cooling or heating.

The decarboxylation of compounds of the formula (V) in which each of X_8 and X_9 represents carboxy and X_{10} has the same meaning as R_2 is carried out while heating, for example in a temperature range of from approximately 100° to approximately 300°C, optionally in the presence of a transition metal or an alloy thereof, for example copper or copper bronze, or an amine, such as a basic nitrogen heterocycle, for example pyridine or quinoline, or an alkylamine, such as tri-lower alkylamine, and results in compounds of the formula (I) in which R_1 represents carboxy, or salts thereof.

The reductive conversion, with hydrogen, of X_{10} in compounds of the formula (V) in which X_8 has the same meaning as R_1, X_9 has the same meaning as R_2 and X_{10} represents hydroxy, functionally modified hydroxy, dialkylamino, or mercapto substituted by a hydrocarbon radical, especially lower alkylthio, is carried out, for example, by hydrogenation in the presence of a hydrogenation catalyst, such as an element of sub-group VIII of the Periodic Table or a derivative, for example an oxide, thereof, wherein the catalyst may optionally be supported on a carrier, such as activated carbon or an alkaline earth metal carbonate or sulphate. The hydrogenation is preferably carried out while cooling or heating, for example between approximately −80° to approximately 200°C, more especially between room temperature and 100°C, approximately in a suitable solvent, for example water, a lower alkanol, such as ethanol or isopropanol, an ether, such as dioxane, a lower alkanecarboxylic acid, such as acetic acid, or a mixture thereof.

There may be mentioned as examples of such catalysts Raney nickel or palladium-on-carbon, and also platinum, platinum oxide or palladium. If necessary, the hydrogenation is carried out in the presence of an acid or, especially, a base. Corresponding acids are protonic acids, such as mineral acids, for example hydrohalic acids, and also carboxylic acids, such as lower alkanecarboxylic acids. There come into consideration as bases, for example, alkali metal hydroxides, carbonates or acetates, amines, such as lower alkylamines, or basic heterocycles, such as pyridine or quinoline.

In corresponding compounds of the formula (V) in which X_{10} represents hydroxy, the hydroxy group can also be converted into hydrogen by means of red phosphorus and/or hydriodic acid while heating, for example at from approximately 100 to approximately 250°C, but advantageously with red phosphorus and hydriodic acid.

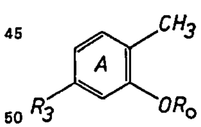
The reductive conversion of hydroxy X_{10} that is esterified by an organic sulphonic acid, such as *p*-toluene-sulphonyloxy, can be carried out by means of a customary reducing agent, such as an alkali metal alloy, for example sodium amalgam, in protic solvent or with an optionally complex hydride, such as a hydride with elements of main group(s) I and/or III, for example lithium borohydride.

Compounds of the formula (V) in which X_9 and X_{10} together represent oxo or thioxo can be reduced to compounds of the formula (I) in which R_2 represents hydrogen by reducing the oxo or thioxo group, for example analogously to the Clemensen reduction, for example with a metal, such as zinc, optionally zinc amalgam, in a protonic acid, such as a mineral acid, for example hydrochloric acid, or especially according to Wolff-Kishner with hydrazine in an (inert high-boiling) solvent, such as an alcohol, optionally under pressure, at elevated temperature and in the presence of a base, such as an alkali metal hydroxide, or according to the variant described by Huang-Minlon in a high-boiling solvent, such as a corresponding ethylene glycol. The reduction with hydrazine can also be carried out with a base, such as an alkali metal alkoxide, for example in dimethyl sulphoxide at room temperature.

It is also possible to obtain compounds of the formula (I) in which R_2 represents hydrogen by reducing, for example, compounds of the formula (V) in which X_9 and X_{10} together represent optionally substituted hydrazono, especially *p*-toluenesulphonylhydrazono, and X_8 has the same meaning as R_1, by means of a suitable reducing agent, especially an optionally complex hydride, for example a hydride of elements of main group(s) I and/or III, for example sodium borohydride.

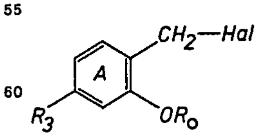
Starting compounds of the formula (V) in which X_8 has the same meaning as R_1 and X_9 and X_{10} together form the group $= R_2'$ or a tautomeric form thereof can be converted, for example by catalytic hydrogenation, into compounds of the formula (I) in which R_2 is other than hydrogen. The hydrogenation can be carried out in a manner known *per se* in the aforedescribed manner using the catalysts mentioned. In principle, the corresponding reduction methods as described in Houben-Weyl, Vol. 4/1c (1980) and Vol. 4/1d (1981), for example, are suitable.

Starting materials of the formula (V) in which each of X_8 and X_9 represents carboxy and X_{10} has the same meaning as R_2 can be produced according to processes known *per se*. For example, compounds of the formula



(Va)

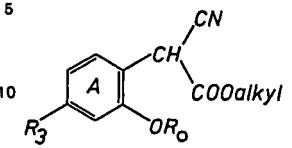
or salts thereof are used as starting materials and are reacted with a halogenation agent, for example with N-bromosuccinimide in the presence of a radical former, such as benzoyl peroxide, at elevated temperature. In the resulting compounds of the formula



(Vb)

or salts thereof in which Hal represents halogen, especially bromine or chlorine, the halogen atom is substituted by the cyano group by reaction with an alkali metal cyanide, such as sodium

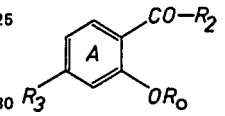
cyanide. There then follows the reaction with a dialkyl carbonate, for example diethyl carbonate, in the presence of a base, such as an alkali metal, for example sodium, to form compounds of the formula



(Vc)

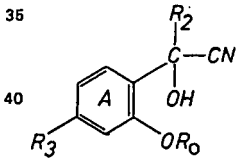
in which alkyl represents an alkyl radical corresponding to the dialkyl carbonate, or salts thereof. If desired, the radical R_3 other than hydrogen is then introduced by reaction with compounds of the formula R_3-Hal (Vd) in the presence of a base, such as an alkali metal alcoholate, for example sodium methoxide. The subsequent hydrolysis of the cyano group and of the alkoxycarbonyl group results in the desired compounds of the formula (V).

Starting materials of the formula (V) in which X_9 has the same meaning as R_1, X_9 has the same meaning as R_2 and X_{10} represents hydroxy or functionally modified hydroxy are obtained, for example, by reacting compounds of the formula



(Ve)

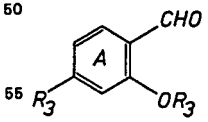
or salts thereof with cyanides, such as sodium cyanide, in the presence of a protonic acid, such as hydrochloric acid, to form cyanohydrins of the formula



(Vf)

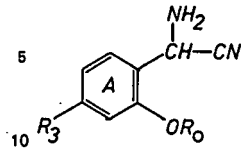
or salts thereof. In the next reaction step, the cyano group is solvolysed to R_1 and, if desired, the hydroxy group or R_o is esterified or etherified.

Corresponding starting materials of the formula (V) in which X_{10} represents secondary amino are obtained, for example, by reacting compounds of the formula



(Vg)

or salts thereof with a solution of ammonium chloride and sodium cyanide or with sodium cyanide and ammonium carbonate, with subsequent hydrolysis of the resulting hydantoin by means of an alkali metal hydroxide and, if desired, subsequent insertion of the radical R_2 other than hydrogen, by reaction with compounds of the formula (Vd) in the presence of bases, for example sodium methoxide, into resulting compounds of the formula

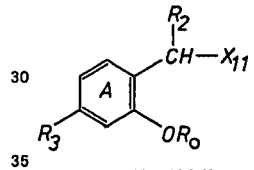


(Vh)

or salts thereof. In the next reaction step, the amino group can be converted into a secondary amino group. It is thus possible, for example by reaction with formic acid/formaldehyde, to obtain a dimethylamino group. Finally, the cyano group is converted into the radical R_1 in known manner by solvolysis.

For the manufacture of starting materials of the formula (V) in which X_9 has the same meaning as R_1 and X_9 and X_{10} together form the group $=R'_2$ or a tautomeric form thereof, compounds of the formula (Vf) or salts thereof are used as starting materials. These are dehydrated, for example by means of an acid, such as a mineral acid, for example sulphuric acid or phosphoric acid or polyphosphoric acid, a salt thereof, such as potassium bisulphate, or an anhydride thereof, for example thionyl choride, to form the corresponding compounds of the formula (V), and the cyano group is converted into R_1 by solvolysis.

Another method of manufacturing compounds of the formula (I) in which R_1 represents carboxy or esterified carboxy comprises, in compounds of the formula



(VI)

or salts thereof in which X_{11} represents a radical that can be converted into R_1 by oxidation, converting X_{11} into R_1 by oxidation and, if desired, converting a salt obtainable according to the process into the free compound or into a different salt, converting a free compound obtainable according to the process into a different free compound or into a salt and/or, if desired, separating an isomeric mixture obtainable according to the process into its components.

A radical X_{11} that can be converted into R_1 by oxidation is, for example, hydroxymethyl; hydroxymethyl esterified by a carboxylic acid, such as optionally substituted lower alkanecarboxylic acid, for example acetic acid; hydroxymethyl etherified by an alcohol, such as lower alkanol, for example methanol or ethanol; formyl; hydrated or acetalised formyl, or represents a group of the formula $-CH=CH-X_{14}$, $-CH=C(Ar)_2$, $-CH(OH)-CH(OH)-X_{14}$, $-CH(OH)-CO-X_{14}$, $-CH(OH)-CO-O-X_{14}$, $-CO-CO-X_{14}$, $-CH(NH_2)-CO-X_{14}$ or $-CO-COOH$, in which X_{14} represents hydrogen, an phatic radical, for example an optionally substituted lower alkyl radical, or an aryl radical, and there is to be understood by Ar an aryl radical, and by the latter, for example, an optionally substituted phenyl radical.

The oxidation is carried out in a manner known *ser se* using suitable oxidising agents in an inert solvent or diluent and, if necessary, while cooling or heating, for example at from approximately 0° to approximately 150°C.

Suitable oxidising agents are, for example, oxygen, ozone, peroxides, such as hydrogen peroxide, or peroxides or organic carboxylic acids, such as trifluoroperacetic acid or *m*-chloroperbenzoic acid, oxidising compounds of transition metals, especially those of elements of sub-group I, VI, VII or VIII of the Periodic Table, such as copper compounds for example copper chromite, such as silver compounds, for example silver (I) oxide or silver picolinate, chromium compounds, for example chromyl chloride, chromium trioxide, alkali metal chromates or dichromates, such as potassium bichromate, manganese compounds, for example manganese dioxide or alkali metal permanganates, or halogen-oxygen compounds, for example alkali metal iodates or periodiates, further, halogen, for example bromine or chlorine, halogen-oxygen compounds, for example alkali metal hypochlorites, iodates, periodates or periodic acid, nitric acids or anhydrides, for example nitric acid or corresponding anhydrides of sulphuric acid. If necessary, it is also possible to use mixtures of oxidising agents.

The oxidation is frequently carried out in the presence of bases, such as alkali metal

hydroxides or carbonates, for example sodium hydroxide or carbonate, or amines, for example cyclic amines, for example pyridine, or lower alkylamines, for example triethylamine, or in the presence of protonic acids, such as mineral acids, for example sulphuric acid or a hydrohalic acid, or organic caboxylic acids, such as lower alkanecarboxylic acids, for example acetic acid, and optionally while cooling or heating.

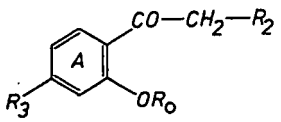
There come into consideration as solvents or diluents, for example, water, ethers, such as dioxan or ethylene glycol diethyl ether, ketones, such as acetone, alcohols, such as the lower alkanols methanol or ethanol, amides, such as dimethylformamide, carboxylic acids, such as lower alkanecarboxylic acids, acetic acid, or mixtures thereof.

Hydroxymethyl or hydroxymethyl X_{11}, esterified by a carboxylic acid is oxidised to carboxy, for example by heating with potassium dichromate in sulphuric acid, the oxidation proceeding by way of the formyl stage. Formyl, hydrated or acetalised, is converted into carboxy, for example by means of silver (I) oxide in sodium hydroxide solution or with the aid of potassium permanganate in soda solution while heating, whilst the group X_{11} $-CH=CH-X_{14}$ is oxidised to carboxy, for example by means of ozone and hydrogen peroxide by way of the formyl stage. Etherified hydroxymethyl can be converted into esterified carboxy, for example with potassium permanganate in aqueous pyridine at room temperature.

The formyl group X_{11} may advantageously be formed *in situ* or freed from a functionally modified form in the course of oxidation reactions. The *in situ* formation of formyl is effected especially from those radicals X_{11} which represent especially hydroxymethyl or groups of the formulae $-CH=CH-X_{14}$, $-CH(OH)-CH(OH)-X_{14}$, or $-CH(OH)-CO-X_{14}$, and also $-CH=C(Ar)_2$, $-CO-CO-X_{14}$, $-CH(OH)-CO-OX_{14}$ or $-CH(NH_2)-CO-X_{14}$. The liberation of the formyl group X_{11} is effected, for example, from one of its acetals or imines or from other formyl-protecting groups. Acetalised formyl is, for example, formyl acetalised by lower alkanols or a lower alkanediol, such as di-lower alkoxymethyl, for example dimethoxy- or diethyoxy-methyl, or lower alkylenedioxy-methyl, for example ethylene- or trimethylene-dioxymethyl. Formyl can also be freed from the corresponding thioacetals. Imines are, for example, optionally substituted N-benzylimines or N-(2-benzothiazolyl)-imine.

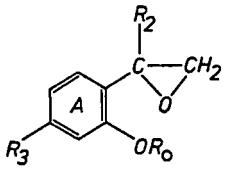
Oxidation of the remaining radicals X_{11} to carboxy can advantageously be carried out *in situ*, often by way of the formyl stage, and accordingly, for example, as follows: $X_{11}-CH(OH)-COO-X_{14}$, $-CH=CH-X_{14}$ and $-CH(OH)-CH(OH)-X_{14}$, for example by means of sodium periodate in the presence of catalytic amounts of potassium permanganate; X_{11} hydroxymethyl, $-CH(NH_2)-CO-X_{14}$, $-CH(OH)-CO-X_{14}$ and $CO-CO-X_{14}$, for example by means of potassium permanganate solution rendered alkaline with sodium carbonate, potassium dichromate solution acidified with sulphuric acid, or concentrated nitric acid; X_{11} $-CH=C(Ar)_2$ in which Ar represents in each case especially phenyl, analogously to the method described by Barbier-Wieland, for example with chromium trioxide in glacial acetic acid; and X_{11} $-CO-COOH$, for example by treatment with concentrated sulphuric acid or with hydrogen peroxide in dilute sodium hydroxide solution (decarbonylation).

Starting materials of the formula (VI) in which X_{11} represents hydroxymethyl, esterified or etherified hydroxymethyl can be obtained, for example, by reacting compounds of the formula



(VIa)

with a mixture of trimethylsulphoniummethyl sulphate and sodium methoxide, for example at room temperature, in acetonitrile. In the resulting compounds of the formula

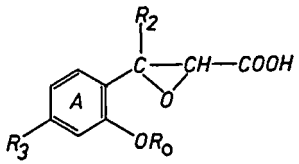


(VIb)

in the following reaction step the oxirane ring is opened, for example in the presence of a Lewis

acid, such as aluminium chloride, to form the compound of the formula (VI) in which X_{11} represents formyl. In optional additional reactions the formyl can, if desired, be acetalised or reduced to hydroxymethyl in a manner known *per se*. The hydroxymethyl group can in turn, if desired, be esterified or etherified.

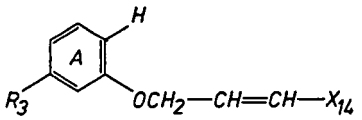
Corresponding starting materials of the formula (VI) can also be obtained by, for example, treating compounds of the formula (VIa) with haloacetonitrile, for example chloroacetonitrile, at low temperatures and in the presence of a base, such as an alkali metal alkoxide, for example sodium methoxide, and hydrolysing the resulting glycidonitrile, for example with the aid of a base, such as an alkali metal hydroxide, for example sodium hydroxide solution, while heating. Then, the resulting compounds of the formula



(VIc)

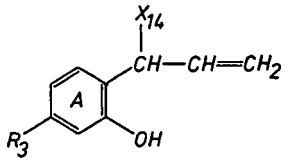
are decarboxylated while heating, for example at the reflux temperature of toluene, resulting in compounds of the formula (VI) in which X_{11} represents formyl. By means of optional additional steps, the formyl can be acetalised or reduced to hydroxymethyl in a manner known *per se*. The latter can in turn, if desired, be esterified or etherified.

Starting materials of the formula (VI) in which X_{11} represents a group of the formula $-CH=CH-X_{14}$ can be produced by heating, for example, compounds of the formula



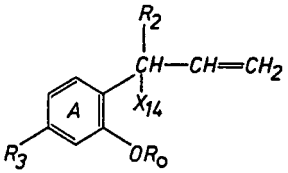
(VId)

at high temperatures, for example at 250°C and then, in the resulting compounds of the formula



(VIe)

if desired converting the hydroxy group into OR_o, for example by esterification, for example acetylation with acetic anhydride/pyridine, and/or, if desired, introducing the radical R_3 by reaction with a compound of the formula R_3-H in the presence of a base, for example sodium amide in liquid ammonia. The subsequent oxidation of the resulting compounds of the formula



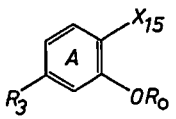
(VIf)

with ozone and a peroxide, for example 30% strength hydrogen peroxide, at room temperature, results in compounds of the formula (I) in which R_1 represents carboxy.

For the manufacture of compounds of the formula VI in which X_{11} represents a radical that can be converted into R_1 by oxidation, for example a salicyclic acid derivative corresponding to the formula I is used as starting material and the carboxy group is reduced to the hydroxymethyl group, there being used as reducing agent, for example, a complex hydride, such as lithium aluminium hydride. After substitution of the hydroxy group by a halogen atom, for example by treatment with a halogenation reagent, such as thionyl chloride, the resulting halomethyl compound is reacted, for example, with a halide of the formula Hal-X_{11} in the presence of magnesium and copper (I) iodide. Preferred compounds of the formula Hal-X_{11} are, for example, those in which X_{11} represents a group of the formula $-CH=CH-X_{14}$ or $-CH=C(Ar)_2$. From the resulting compounds of the formula VI in which X_{11} represents $-CH=CH-X_{14}$, there are obtained, for example by ozonolysis and by cleaving the ozonide by zinc/glacial acetic acid to form formyl X_{11}, or by hydroxylation of the double bond, for example with osmium tetroxide, by partial or complete oxidation of the hydroxy compounds, corresponding oxo derivatives or compounds in which X_{11} represents one of the following groups: $-CH(OH)-CH(OH)-X_{14}$, $-CH(OH)-CO-X_{14}$ or $-CO-CO-X_{14}$.

The corresponding α-ketocarboxylic acid of the formula VI, i.e. X_{11} represents a group of the formula $-CO-COOH$, can be obtained by treating, for example, a salicyclic acid derivative corresponding to the formula ((I) with phosgene, and reacting the resulting acid chloride, for example, with copper (I) cyanide or sodium cyanide and hydrolysing the cyano group to the carboxy group; by esterification of the latter it is also possilbe to obtain compounds of the formula VI in which X_{11} represents the group $-CO-CO-X_{14}$.

A further method of manufacturing compounds of the formula (I) comprises, in a compound of the formula



(VIII)

or a salt thereof in which X_{15} represents a radical that can be converted into a group of the formula $-CH(R_2)-R_1$, converting X_{15} into a group of the formula $-CH(R_2)-R_1$ by rearrangement and, if desired, converting a salt obtainable according to the process into the free compound or into a different salt, converting a free compound obtainable according to the process into a different free compound or into a salt and/or, if desired, separating an isomeric mixture obtainable according to the process into its components.

Compounds of the formula (VIII) in which X_{15} represents a group of the formula

$-CH(R_2)-C(=N-\overset{\oplus}{N}=N)-X_{16}$

or $-CH(R_2)-C(=N-OH)-X_{16}$, and X_{16} represents an optionally substituted aliphatic radical can be rearranged, according to the Schmidt or Beckmann rearrangement, to form N-mono-substituted carbamoyl (R_1) compounds of the formula (I). The Schmidt or Beckmann rearrangement is carried out in a manner known *per se*. Thus, for example, the respective azides or oximes are treated with acidic catalysts, such as strong protonic acids, for example sulphuric acid, inorganic acid halides, for example phosphorus (V) chloride, or sulphochlorides, for example benzenesulphochloride, optionally in an inert solvent, such as a halogenenated hydrocarbon, for example the halo-lower alkane chloroform, or an aromatic compound, for example benzene, in a temperature range of from approximately − 30 to approximately 150°C.

Compounds of the formula (VIII) in which X_{15}represents a group of the formula $-CH(R_2)-CO-CH_2-N_2$ can be rearranged by analogous methods in accordance with the Wolff rearrangement to form compounds of the formula (II) in which R_1 represents optionaly esterified or amidated carboxy. Thus the reaction is carried out, for example, while heating and/or irradiating with energy-rich light, for example UV light, and/or in the presence of a catalyst, for example a noble metal or noble metal oxide, such as copper, silver or silver oxide, in an inert solvent, such as an ether, for example dioxan or tetrahydrofuran, the temperature advantageously being in the range of from approximately 0° to approximately 150°C. By adding water, alcohol, ammonia or amine, the reaction can be directed so as to form free carboxylic acid, or esterified or amidated carboxylic acid R_1.

Compounds of the formula (VIII) in which X_{15} represents a group of the formula

$-CO-CH_2-Hal$ and Hal represents halogen, such as chlorine, bromine, or also iodine, can be converted in a manner known *per se* analogously to the Faworskij rearrangement into compounds of the formula (I) in which R_1 represents carboxy and R_2 represents hydrogen. The corresponding rearrangement can be carried out, for example, by heating with strong bases, such as alkali metal hydroxides, or by treatment with Ag(I) compounds, such as silver (I) oxide or silver (I) nitrate while heating in a solvent, such as water and/or lower alkanol.

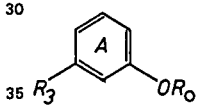
The oxidative rearrangement of compounds of the formula (VIII) in which X_{15} represents a group of the formula $-CO-CH_2-R_2$ is carried out, for example, by means of the oxidising agent thallium (III) nitrate, the operation preferably being carried out in an alcohol, such as a lower alkanol, optionally in the presence of traces of strong protonic acid, such as perchloric acid, or in the presence of trimethyl orthoformate. Also, an inert solvent, such as an optionally halogenated hydrocarbon, for example hexane- or chloroform, or an ether, for example dioxan, may be used. The oxidising agent may also be supported on a suitable carrier [Lit. J. Am. Chem. Soc. *98*, 6750 (1976)].

If the reaction is carried out in a lower alkanol, compounds of the formula (I) are obtained in which R_1 represents lower alkoxycarbonyl.

The oxidative rearrangement of compounds of the formula (VIII) in which X_{15} represents a group of the formula $-CO-CH_2-R_2$ and R_2 represents hydrogen analogously to the Willgerodt-Kindler reaction, is carried out with aqueous ammonium polysulphide, generally under pressure, or with sulphur and a primary or tertiary amine in an inert solvent and optionally while heating. In this process compounds of the formula (I) are obtained in which R_1 represents amidated carboxy, or a corresponding thiocarbamoyl or ammonium carboxylate, and R_2 represents hydrogen. A solvent is, for example, an ether, such as dioxane or tetrahydrofurane, or a lower alkanol, such as ethanol. Preferably, the reaction is carried out by boiling under reflux.

The starting materials of the formula (VIII) are known or are produced according to analogous processes.

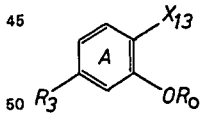
A general process for the manufacture of compounds of the formula (VIII) comprises, for example, reacting a compound of the formula



(VIIIa)

or a salt thereof with a compound of the formula Hal-X_{15} in which Hal represents halogen, such as chlorine or bromine. The reaction is carried out, for example, in the presence of a strong acid, such as polyphosphoric acid, or especially in the presence of a Lewis acid, such as aluminium chloride.

A further process variant for the manufacture of compounds of the formula (I) or salts or isomers thereof comprises, in a compound of the formula

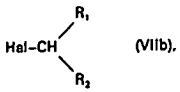


(VII)

in which X_{13} represents a radical that can be converted into a group of the formula $-CH(R_2)-R_1$ (VIIa), or in a salt or isomer thereof, converting the radical X_{13} into a group of the formula (VIIa) and, if desired, converting a salt obtainable according to the process into the free compound or into a different salt, converting a free compound obtainable according to the process into a salt or into a different free compound, and/or, if desired, separating an isomeric mixture obtainable according to the process into its components.

A radical X_{13} that can be converted into a group of the formula (VIIa) is, for example, a group of the formula $-Mg-Hal$ or $-CH(R_2)-Mg-Hal$, in which in each case Hal represents halogen, especially chlorine or bromine.

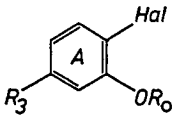
The group of the formula (VIIa) is introduced in a manner known *per se* into a compound of the formula (VII) in which X_{13} represents the group $-Mg-Hal$. For example, a corresponding compound of the formula (VII) is reacted with a compound of the formula



(VIIb),

or a salt thereof, in which Hal represents halogen. The reaction is carried out if necessary while cooling in an inert solvent or diluent, such as an ether, for example a di-lower alkyl ether or cyclic ether, optionally under a protective gas, such as nitrogen, preferably at a temperature range of from approximately −80° to approximately the boiling temperature of the solvent.

Corresponding starting materials of the formula (VII) in which X_{13} represents the group −Mg−Hal, or salts or isomers thereof, are manufactured according to methods known *per se*, for example by reacting compounds of the formula

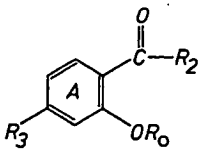


(VIId)

or salts thereof with magnesium in an ether, such as tetrahydrofuran. The corresponding compounds of the formula (VIId) are known or can be obtained in an analogous manner.

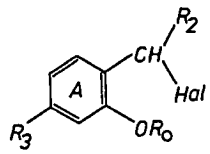
It is possible to introduce the group of the formula (VIIa) in which R_1 represents carboxy into compounds of the formula (VII) in which X_{13} represents the group of the formula $-CH(R_2)-Mg-Hal$, or into salts or isomers thereof, by treating corresponding compounds of the formula (VII) with carbon dioxide. The reaction is carried out if necessary while cooling in an inert solvent, such as an ether, for example a di-lower alkyl ether or a cyclic ether, and optionally under a protective gas, for example nitrogen.

Corresponding starting materials of the formula (VII) in which X_{13} represents a group of the formula $-CH(R_2)-Mg-Hal$ can be obtained, for example, by, in a compound of the formula



(VIIe)

or a salt thereof, reducing the oxo group to a hydroxy group with a reducing agent, such as an optionally complex hydride, for example lithium aluminium hydride or sodium borohydride, while heating gently. The hydroxy group is subsequently substituted by halogen, for example by treating with a phosphorus halide, for example phosphorus bromide or chloride, if necessary while cooling, for example at 0°C. A resulting compound of the formula



(VIIf)

or a salt thereof is then reacted with magnesium to form a corresponding compound of the formula (VII), the reaction being carried out in an inert solvent, for example an ether, such as dioxan.

A compound of the formula (I) obtainable according to the invention can be converted in a manner known *per se* into a different compound of the formula (I).

If the ring A is substituted by lower alkylthio, it is possible to oxidise this in customary

manner to form the corresponding lower alkane-sulphinyl or -sulphonyl. There come into consideration as suitable oxidising agents for the oxidation to the sulphoxide stage, for example, inorganic peracids, such as peracids of mineral acids, for example periodic acid or persulphuric acid, organic peracids, such as corresponding percarboxylic or persulphonic acids, for example performic, peracetic, trifluoroperacetic or perbenzoic acid or *p*-toluenepersulphonic acid, or mixtures of hydrogen peroxide and acids, for example a mixture of hydrogen peroxide and acetic acid.

The oxidation is often carried out in the presence of suitable catalysts; there may be mentioned as catalysts suitable acids, such as optionally substituted carboxylic acids, for example acetic acid or trifluoroacetic acid, or transition metal oxides, such as oxides of elements of sub-group VII, for example vanadium, molybdenum or tungsten oxide. The oxidation is carried out under mild conditions, for example at temperatures of from approximately −50° to approximately +100°C.

Th oxidation to the sulphone stage can also be carried out correspondingly with dinitrogen tetroxide as the catalyst in the presence of oxygen at low temperatures, as can the direct oxidation of the lower alkythio to form the lower alkanesulphonyl. In this case, however, the oxidising agent is normally used in excess.

If the ring A of the formula I is substituted by lower alkane-sulphinyl or -sulphonyl, it is possible to reduce this according to methods known *per se* to the corresponding lower alkylthio compound, and, when using lower alkanesulphonyl derivatives as starting materials, also to reduce to lower alkanesulphinyl. Suitable reducing agents are, for example, catalytically activated hydrogen, there being used noble metals or oxides, such as palladium, platinum or rhodium or their oxides, optionally supported on a suitable carrier, such as activated carbon or barium sulphate. Also suitable are reducing metal cations, such as tin (II), lead (II), copper (I), manganese (II), titanium (II), vanadium (II), molydenum (III) or tungsten (III) compounds, hydrogen halides, such as hydrogen chloride, bromide or iodide, hydrides, such as complex metal hydrides, for example lithium aluminium hydride, sodium borohydride, tributyltin hydride, phosphorus compounds, such as phosphorus halides, for example phosphorus trichloride, phosphorus tribromide, phosphorus pentachloride or phosphorus oxychloride, phosphines, such as triphenylphosphine, or phosphorus pentasulphide-pyridine, or sulphur compounds, such as mercaptans, thio acids, such as thiophosphoric acids or dithiocarboxylic acids, dithionite or sulphur/oxygen complexes, such as an iodine/pyridine/sulphur dioxide complex.

If the aromatic ring contains as substituent a hydrogen atom, this can be replaced by a halogen atom in customary manner by means of a halogenation agent.

Thus the substitution of hydrogen by bromine is carried out, for example, by bromination with bromine analogously to "Methoden der Organischen Chemie", Houben-Weyl (4th edition), vol. 5/4, page 233–249, in an inert solvent. Bromination can also be carried out using the following btomination agents: hypobromic acid, acylhypobromites or other organic bromine compounds, for example N-bromosuccinimide, N-bromoacetamide, N-bromophthalimide, pyridinium perbromide, dioxan dibromide, 1,3-dibromo-5,5-dimethylhydantoin, and 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one.

The corresponding chlorination can be carried out, for example, as described in Houben-Weyl (4th edition), volume 5/3, page 651–673; preferably with elementary chlorine, for example in a halogenated hydrocarbon, such as chloroform, and while cooling, for example to approximately −10° to approximately +10°C.

The replacement of hydrogen by iodine can be carried out, for example, with elemental iodine in the presence of mercury oxide or nitric acid. Instead of elemental iodine it is possible to use as iodising agent, for example, an alkali metal iodide in the presence of a thallium (III) difluoroacetate according to Tetrahedron Letters (1969), page 2427.

Also, the benzo moiety of the ring system and/or an additional aromatic ring can be alkylated, for example with a lower alkanol, or a lower alkylhalide or a phosphoric acid lower alkyl ester in the presence of Lewis acids. (Friedel-Crafts alkylation). In a compound of the formula (I) in which the aromatic ring contains bromine, the bromine can, for example, be replaced by lower alkyl by reaction with a lower alkylbromide in the presence of an alkali metal.

If the aromatic ring contains as substituent a hydrogen atom, this can be exchanged in a manner known *per se* for an acyl group. Thus, for example, the introduction of the acyl group can be carried out analogously to Friedel-Crafts acylation (cf. G. A. Olah, Friedel-crafts and Related Reactions, vol. 1, Interscience, New York, 1963–1965), for example by reacting a reactive functional acyl derivative, such as a halide or anhydride, of an organic carboxylic acid in the presence of a Lewis acid, such as aluminum chloride, antimony (III) or (V) chloride, iron (III) chloride, zinc (II) chloride or boron trifluoride.

If the aromatic ring contains hydroxy as substituent, then the hydroxy can be etherified in a manner known *per se*. The reaction with an alcohol component, for example with a lower alkanol, such as ethanol, in the presence of acids, for example a mineral acid, such as sulphuric acid, or in the presence of dehydrating agents, such as dicyclohexyl carbodiimide, results in

lower alkoxy. Conversely, ethers can be split into phenols by treatment with acids, such as mineral acids, for example a hydrohalic acid, such as hydrobromic acid, or Lewis acids, for example halides of elements of main group III, such as boron tribromide, or by treatment with pyridine hydrochloride or thiophenol.

Furthermore, hydroxy can be converted into lower alkanoyloxy, for example by reaction with a desired lower alkanecarboxylic acid, such as acetic acid, or a reactive derivative thereof, for example in the presence of an acid, such as a protonic acid, for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, or a benzenesulphonic acid, in the presence of a Lewis acid, for example boron trifluoride etherate, or in the presence of a water-binding agent, such as dicyclohexyl carbodiimide. Conversely, esterified hydroxy can be solvolysed, for example by base catalysis, to form hydroxy.

Free, esterified and amidated carboxy groups R_1 can be converted one into another, for example a free carboxy group can be converted in customary manner into an esterified carboxy group R_1, preferably by reaction with a corresponding alcohol or with a reactive derivative of the corresponding alcohol, such as a carboxylic, phosphorous, sulphurous or carbonic acid ester, for example a lower alkanecarboxylic acid ester, tri-lower alkylphosphite, di-lower alkylsulphite or the pyrocarbonate, or a mineral acid or sulphonic acid ester, for example hydrochloric, hydrobromic, or sulphuric acid ester, benzenesulphonic acid ester, toluene-sulphonic acid ester or methanesulphonic acid ester, or with an olefin derived therefrom.

The reaction with the corresponding alcohol is carried out advantageously in the presence of an acidic catalyst, such as a protonic acid, for example hydrochloric or hydrobromic acid, sulphuric acid, phosphoric acid, boric acid, benzenesulphonic acid and/or toluenesulphonic acid, or a Lewis acid, for example boron trifluoride etherate, in an inert solvent, especially an excess of the alcohol used, and, if necessary, in the presence of a water-binding agent and/or with distillative, for example azeotropic, removal of the water of reaction and/or at elevated temperature.

The reaction with a reactive derivative of the corresponding alcohol can be carried out in customary manner, using as starting material a carboxylic, phosphorous, sulphurous or carbonic acid ester, for example in the presence of an acidic catalyst, such as one of those mentioned above, in an inert solvent, such as an aromatic hydrocarbon, for example in benzene or toluene, or in an excess of the alcohol derivative used or of the corresponding alcohol, if necessary with removal by, for example azeotropic, distillation of the water of reaction. Using as starting material a mineral acid ester or a sulphonic acid ester, the acid to be esterified is reacted advantageously in the form of a salt, for example the sodium, potassium or calcium hydroxide or carbonate, in the presence of a basic condensation agent, such as an inorganic base, for example sodium, potassium or calcium hydroxide or carbonate, or a tertiary organic nitrogen base, for example triethylamine or pyridine, if necessary in an inert solvent, such as one of the above tertiary nitrogen bases or a polar solvent, for example dimethylformamide, and/or at elevated temperature.

The reaction with an olefin can be carried out, for example, in the presence of an acidic catalyst, for example a Lewis acid, for example boron trifluoride, a sulphonic acid, for example *p*-toluenesulphonic acid or, especially, a basic catalyst, for example sodium or potassium hydroxide, advantageously in an inert solvent, such as an ether, for example in diethyl ether or tetrahydrofuran.

A free carboxy group R_1 can furthermore be converted into an amidated carboxy group R_1 by reaction with ammonia, or an amine containing at least one hydrogen atom, in customary manner with dehydration of the ammonium salt formed as intermediate, for example by azeotropic distillation with benzene or toluene or heating in the dry state.

The above-described conversion of free carboxy groups R_1 into esterified or amidated carboxy groups R_1 can, however, also be carried out by first of all converting a compound of the formula I in which R_1 represents carboxy in customary manner into a reactive derivative, for example by means of a halide of phosphorus or sulphur, for example by means of phosphorus trichloride or tribromide, phosphorus pentachloride or thionyl chloride, into an acid halide, or by reaction with a corresponding alcohol or amine into a reactive ester, that is an ester with an electron-attracting structure, such as the esters with phenol, thiophenyl, *p*-nitrophenol or cyanomethyl alcohol, or into a reactive amide, for example the amide derived from imidazole or 3,5-dimethylpyrazole, and then reacting the resulting reactive derivative in customary manner to form the desired group R_1, for example as described below for the transesterification, transamidation or mutual conversion of esterified and amidated carboxy groups R_1, with a corresponding alcohol, ammonia or the corresponding amine containing at least one hydrogen atom.

Furthermore, an esterfied carboxy group R_1 can be converted in customary manner into a free carboxy group R_1, for example by hydrolysis in the presence of a catalyst, for example a basic or acidic agent, such as a strong base, for example sodium or potassium hydroxide, or a mineral acid, for example hydrochloric acid, sulphuric acid or phosphoric acid, or into an amidated carboxy group R_1, for example by reaction with ammonia or the corresponding amine containing at least one hydrogen atom.

An esterified carboxy group R_1 can furthermore be reacted to form a different esterified carboxy group R_1 in customary manner, for example by reaction with a corresponding metal alcoholate, for example the sodium or potassium alcoholate of the corresponding alcohol, or with the alcohol itself, in the presence of a catalyst, for example a strong base, for example sodium or potassium hydroxide, or a strong acid, such as a mineral acid, for example hydrochloric acid, sulphuric acid or phosphoric acid, or an organic sulphonic acid, for example *p*-toluenesulphonic acid, or a Lewis acid, for example boron trifluoride etherate.

An amidated carboxy group R_1 can be converted into the free carboxy group R_1 in customary manner, for example by hydrolysis in the presence of a catalyst, for example a strong base, such as an alkali metal or alkaline earth metal hydroxide or carbonate, for example sodium or potassium hydroxide or carbonate, or a strong acid, such as a mineral acid, for example hydrochloric acid, sulphuric acid or phosphoric acid.

Compounds of the formula (I) containing unsaturated radicals, such as lower alkenyl or lower alkenylene, can be converted in a matter known per se into corresponding compounds containing saturated radicals, For example, the hydrogenation of multiple bonds can be effected by catalytic hydrogenation in the presence of hydrogenating catalysts, which are for example precious metals or a derivative thereof, such as an oxide thereof, such as Nickel, Raney-Nickel, Palladium Platinium oxide, which agents may be supported on suitable carriers, such as carbon or calcium carbonate. The hydrogenation can be effected preferably at a pressure between 1 and approximately −80° to approximately 200°C, more especially between room temperature and approximately 100°C. The reaction is carried out practically in a solvent, such as in water, in a lower alkanol, for example ethanol, isopropanol or n-butanol, in an ether, for example dioxane, or in a lower alkanecarboxylic acid, for example acetic acid.

Conversely in cyclic systems R_1, one or more double bonds can be introduced. For this, suitable dehydrogenating agents can be used, for example elements of the subgroups, preferably of subgroup VIII of the Periodic Table, for example Palladium or Platinium, or derivatives of precious metals, for example ruthenium-triphenylphosphid-chloride, the agents may be supported on a suitable carrier. Further preferred dehydrogenating agents are for example quinones, such as β-benzoquinones, for example tetrachloro-p-benzoquinone or 2,3-dichloro-5,6-dicyano-p-benzoquinone, or anthraquinones, such as phenanthren-9,ω-quinone. Furthermore, N-halogeno-succinimides, such as N-chloro-succinimide, manganese compounds, such as barium manganate or maganese dioxide, and selenium derivatives, such as selenium dioxide or diphenylselenium-tris-trifluoroacetate, can be used.

Salts of compounds of the formula (I) can be manufactured in a manner known *per se*. Thus, for example, acid addition salts of compounds of the formula (I) are obtained by treatment with an acid or a suitable ion exchange reagent. Salts can be converted in customary manner into the free compounds; for example, acid addition salts can be converted by treatment with a suitable basic agent.

As a result of the close relationship between the novel compound in free form and in the form of its salts, hereinbefore and hereinafter the free compound or its salt shall be understood to mean optionally also the corresponding salt or free compound, respectively, where appropriate with regard to meaning and purpose.

The novel compound, including its salts, can also be obtained in the form of its hydrates, or include other solvents used for the crystallisation.

Depending upon the starting materials and methods chosen, the novel compounds may be in the form of one of the possible isomers or in the form of mixtures thereof, for example, depending on the number of asymmetric carbon atoms, in the form of pure optical isomers, such as antipodes, or in the form of mixtures of isomers, such as racemates, mixtures of diastereoisomers or mixtures of racemates.

Resulting mixtures of diastereoisomers and mixtures of racemates can be separated on the basis of the physico-chemical differences between the constituents, in known manner, into the pure isomers, diastereoisomers or racemates, for example by chromatography and/or fractional crystallisation. Resulting racemates can futhermore be resolved into the optical antipodes by known methods, for example by recrystallisation from an optically active solvent, with the aid of micro-organisms or by converting into diastereoisomeric salts or esters, for example by reacting an acidic end product with an optically active base that forms salts with the racemic acid, or with an optically active carboxylic acid or a reactive derivative thereof, and separating the mixture of diastereoisomers obtained in this manner, for example on the basis of their different solubilities, into the diastereoisomers, from which the desired enantiomer can be freed by the action of suitable agents. Advantageously, the more active enantiomer is isolated.

The invention relates also to those embodiments of the process according to which compounds obtainable as intermediates at any stage of the process are used as starting materials and the remaining steps are carried out or a starting material is used in the form of a salt or, especially, is formed under the reaction conditions.

In the process of the present invention it is preferable to use those starting materials which result in the compounds described at the beginning as being especially valuable. The invention relates also to novel starting materials, their use, for example as the active ingredients of medicaments, to formulation processes and to processes for their manufacture.

The starting materials of the formulae II, III, IV, V, VII and VIII, which have been especially developed for the production of the compounds of the invention, the processes for obtaining them and the use thereof, likewise constitute objects of the invention. Preferably compounds of the formula (VI) in which X_{11} denotes optionally esterified or etherified hydroxymethyl or optionally acetalised formyl, process for their manufacture and the use thereof, for example as starting material or as pharmaceutically active compounds, furthermore pharmaceutical preparations and the process for the manufacture of them constitute a prefered subject matter of the invention.

The pharmaceutical preparations according to the invention, which contain the compound according to the invention or pharmaceutically acceptable salts thereof, are for topical application, and also for enteral, such as oral or rectal, and parenteral administration to (a) warm-blooded animal(s) and contain the pharmacological active ingredient alone or together with a pharmaceutically acceptable carrier. The daily dosage of the active ingredient depends on age and the individual condition, and on the method of administration.

The novel pharmaceutical preparations contain, for example, from approximately 10% to approximately 80%, preferably from approximately 20% to approximately 60%, of active ingredient. Pharmaceutical preparations according to the invention for enteral or parenteral administration are, for example, those in dosage unit forms, such as dragées, tablets, capsules or suppositories, and also ampoules. These are manufactured in a manner known *per se*, for example by means of conventional mixing, granuating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical preparations for oral administration can be obtained by combining the active ingredient with solid carriers, optionally granulating a resulting mixture and processing the mixture or granulate, if desired or necessary after the addition of suitable adjuncts, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugar, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatine, tragacanth, methylcellulose and/or polyvinylpyrrolidine, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, cross-linked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Adjuncts are especially flow-regulating agents and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable coatings that are optionally resistant to gastric juices, there being used, *inter alia*, concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in suitable organic solvents or solvent mixtures or, for the production of coatings that are resistant to gastric juices, soluions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments can be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Further pharmaceutical preparations for oral administration are dry-filled capsules consisting of gelatine and also soft, sealed capsules consisting of gelatine and a plasticiser, such as glycerine or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also to add stabilisers.

As rectally administrable pharmaceutical preparations there come into consideration, for example, suppositories which consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols and higher alkanols. It is also possible to use gelatine rectal capsules which contain a combination of the active ingredient with a base material; as base materials there come into consideration, for example, liquid triglycerides, polyethylene glycols and paraffin hydrocarbons.

There are suitable for parenteral administration especially aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, also suspensions of the active ingredient, such as corresponding oily injection suspensions, using suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions containing substances that increase the viscosity, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, optionally, also stabilisers.

There come into consideration as pharmaceutical preparations for topical use especially creams, ointments, pastes, foams, tinctures and solutions that contain from approximately 0.1% to approximately 5% of active ingredient.

Creams are oil-in-water emulsions that contain more than 50% of water. As oily base there are used especially fatty alcohols, for example lauryl, cetyl or stearyl alcohol, fatty acids, for example palmitic or stearic acid, liquid to solid waxes, for example isopropyl myristate, wool waxes or beeswax, and/or hydrocarbons, for example petroleum jelly (petrolatum) or paraffin oil. As emulsifiers there come into consideration surface-active substances having predominantly hydrophilic properties, such as corresponding non-ionic emulsifiers, for example fatty acid esters of polyalcohols, or ethylene oxide adducts thereof, such as polyglycerine fatty acid esters or polyoxyethylene sorbitan fatty acid esters (Tweens), also polyoxyethylene fatty alcohol ethers or polyoxyethylene fatty acid esters, or corresponding ionic emulsifiers, such as alkali metal salts of fatty alcohol sulphates, for example sodium lauryl sulphate, sodium cetyl sulphate or sodium stearyl sulphate, which are customarily used in the presence of fatty alcohols, for example cetyl alcohol or stearyl alcohol. Additives to the aqueous phase are, *inter alia*, agents that reduce the drying out of the creams, for example polyalcohols, such as glycerine, sorbitol, propylene glycol and/or polyethylene glycols, also preservatives, perfumes *etc.*.

Ointments are water-in-oil emulsions that contain up to 70%, but preferably from approximately 20% to approximately 50%, of water or aqueous phases. As fatty phase there come into consideration especially hydrocarbons, for example petroleum jelly, paraffin oil and/or hard paraffins, which, in order to improve the water-binding capacity, preferably contain suitable hydroxy compounds, such as fatty alcohols or esters thereof, for example cetyl alcohol or wool wax alcohols, or wool waxes. Emulsifiers are corresponding lipophilic substances, such as sorbitan fatty acid esters (Spans), for example sorbitan oleate and/or sorbitan isostearate. Additives to the aqueous phase are, *inter alia*, humectants, such as polyalcohols, for example glycerine, propylene glycol, sorbital and/or polyethylene glycol, and also preservatives, perfumes *etc.*.

Fatty ointments are anhydrous and contain as base especially hydrocarbons, for example paraffin, petroleum jelly and/or liquid paraffins, and also natural or partially synthetic fats, for example coconut fatty acid triglyceride, or preferably hardened oils, for example hydrogenated ground nut oil or castor oil, and also fatty acid partial esters of glycerine, for example glycerine mono- and di-stearate, and also, for example, the fatty alcohols, which increase the water-absorbing capacity, emulsifiers and/or additives mentioned in connection with the ointments.

Pastes are creams and ointments containing powder ingredients that absorb secretions, such as metal oxides, for example titanium oxide or zinc oxide, also talc and/or aluminium silicates, the purpose of which is to bind any moisture or secretions present.

Foams are administered, for example, from pressurised containers and are liquid oil-in-water emulsions in aerosol form, halogenated hydrocarbons, such as chlorofluoro-lower alkanes, for example dichlorodifluoromethane and dichlorotetrafluoroethane, being used as propellants. For the oily phase there are used, *inter alia*, hydrocarbons, for example paraffin oil, fatty alcohols, for example cetyl alcohol, fatty acid esters, for example isopropyl myristate, and/or other waxes. As emulsifiers there are used, *inter alia*, mixtures of those emulsifiers having predominantly hydrophilic properties, such as polyoxyethylene sorbitan fatty acid esters (Tweens), and those having predominantly lipophilic properties, such as sorbitan fatty acid esters (Spans). In addition, there may be used customary additives, such as preservatives etc.

Tinctures and solutions generally have an aqueous ethanolic base to which there are added, *inter alia*, polyalcohols, for example glycerine, glycols, and/or polyethylene glycol, as humectants for reducing evaporation, and fat-restoring substances, such as fatty acid esters with lower polyethylene glycols, that is to say lipophilic substances that are soluble in the aqueous mixture, to replace the fatty substances that are taken from the skin by the ethanol, and, if necessary, other adjuncts and additives.

The pharmaceutical preparations for topical application are manufactured in a manner known *per se*, for example by dissolving or suspending the active ingredient in the base or, if necessary, in a part thereof. When processing the active ingredient in the form of a solution, it is usually dissolved in one of the two phases before emulsification; when processing the active ingredient in the form of a suspension, it is mixed with a part of the base after emulsification and then added to the remainder of the formulation.

The dosage of the active ingredient depends on the species of warm-blooded animal, age and individual condition, and on the method of administration. In normal cases, the estimated approximate daily dose in the case of oral administration to a warm-blooded animal weighing approximately 75 kg is from approximately 100 to approximately 800 mg, advantageously divided into several equal partial doses.

The following Examples illustrate the invention described above but are not intended to limit the scope of the invention in any way. Temperatures are given in degrees Centrigrade.

Example 1

5.4 g (0.02 mol) of 5-chloro-3-methyl-6-morpholinobenzofuran-2(3H)-one are dissolved in 40 ml of 1N sodium hydroxide solution at 50°C. After cooling, the reaction mixture is washed with ether and the pH of the aqueous phase is then adjusted to 2.0 with 1N hydrochloric acid. The resulting oil is taken up in ether.

After evaporation of the ether, 2-(5-chloro-2-hydroxy-4-morpholinophenyl)-propionic acid is obtained in the form of colourless crystals having a melting point of from 198 to 200°C.

The starting material can be manufactured as follows:

A hot solution of 80 g (2 mol) of sodium hydroxide solution in 200 ml of water is added in portions, while stirring, to a mixture of 341 g (2 mol) of the hydrochloride of imidazo [1,2-a] pyridin-2-(3H)-one in 700 ml of water. A solution of 250.7 g (2.16 mol) of maleic acid in 600 ml of water is then added dropwise in such a manner that the internal temperature of the reaction mixture remains at between 40°C and 45°C. After 30 hours at room temperature (20 to 25°C), the reaction mixture is cooled to 5°C, the precipitate that has formed is filtered off, the filtrate is concentrated to approximately half *in vacuo* and the product that precipitates is filtered with suction. The combined residues are washed with a small amount of cold methanol and dried *in vacuo* at 50°C. 400 g of 3-(1,2-dicarboxyethyl)-imidazo[1,2-a]pyridin-2(3H)-one having a melting point of 193°C (decomp.) are obtained. The resulting product is stirred at room temperature for 6 hours with 650 ml of concentrated hydrochloric acid. After the mixture has cooled to 5°C, the precipitate is filtered off, the filtrate is concentrated *in vacuo* to approximately half and the product that precipitates is filtered with suction. The combined residues are washed with acetone and dried *in vacuo* at 50°C. The hydrochloride of 3-(1,2-dicarboxyethyl)-imidazo[1,2-a]pyridin-2(3H)-one, having a melting point of 205°C (decomp.), is thus obtained.

A mixture of 114.7 g (0.4 mol) of the hydrochloride of 3-(1,2-dicarboxyethyl)-imidazo[1,2-a]pyridin-2(3H)- one, 36.4 g (0.52 mol) of methyl vinyl ketone, 150 ml of methanol and 150 ml of water is stirred at room temperature for 36 hours and then concentrated to dryness by evaporation *in vacuo* at approximately 45°C. The resulting crude product is taken up in 300 ml of glacial acetic acid, 15 g of sodium acetate are added and the whole is boiled under reflux until the evolution of CO_2 is complete. The solvent is then removed *in vacuo*, a mixture of 150 ml of 6M sulphuric acid and 150 ml of tetrahydrofuran is added to the residue and the whole is maintained at 60°C for 8 hours. After the removal of the tetrahydrofuran *in vacuo*, the reaction mixture is diluted with water, extracted with methylene chloride and filtered over silica gel. Distillation of the crude product under a high vacuum (115°C to 125°C/8 Pa) gives 4-methyl-3-(3-oxo-butyl)-maleic acid anhydride in the form of a spectroscopically uniform pale yellow oil.

A mixture of 18.2 g (0.1 mol) of 4-methyl-3-(3-oxobutyl)-maleic acid anhydride and 22 g (0.105 mol) of morpholinium benzoate in 400 ml of benzene is heated under reflux on a water separator for 48 hours. The benzene is removed *in vacuo*, the residue is taken up in methylene chloride and the organic phase is extracted twice with saturated sodium bicarbonate solution. The crude product remaining after drying and after removal of the methylene chloride is chromatographed with petroleum ether/ether over silica gel. Pale yellow crystals are obtained which are recrystallised from methylene chloride/ether.

3-methyl-6-morpholinobenzofuran-2(3H)-one having a melting point of from 118 to 121°C is thus obtained.

A cold solution of chlorine in chloroform is added drowise to a mixture of 14.7 g (0.063 mol) of 3-methyl-6-morpholinobenzofuran-2(3H)-one in 100 ml of chloroform at from 0 to 5°C, while stirring, until no educt is visible on a thin-layer chromatograph. The reaction mixture is diluted with methylene chloride and washed successively with 10% sodium thiosulphate solution, dilute sodium bicarbonate solution and water. The crude product remaining after the organic phase has been dried and concentrated by evaporation is chromatographed with petroleum ether/ether over silica gel. After recrystallisation of the pure fractions from ether/petroleum ether, 5-chloro-3-methyl-6-morpholinobenzofuran-2(3H)-one having a melting point of from 103 to 105°C is obtained.

Example 2

A mixture of 19.6 g (0.1 mol) of 4-methyl-3-(2-methyl-3-oxobutyl)-maleic acid anhyride and 21.3 g (0.11 mol) of pyrrolidinium benzoate in 400 ml of benzene is heated under reflux on a water separator for 30 hours. The benzene is removed *in vacuo* and the residue is partitioned between ether and saturated sodium bicarbonate solution. The crude product remaining after the organic phase has been dried and concentrated by evaporation is chromatographed over silica gel. Elution with petroleum ether/ether and subsequent recrystallisation of the pure fractions from ether/petroleum ether gives 3,5-dimethyl-6-(pyrrolidin-1-yl)-benzofuran-2(3H)-one having a melting point of from 67 to 69°C. By increasing the polarity of the eluant (ether/methanol) 2-[2-hydroxy-5-methyl-4-(pyrrolidin-1-yl)-phenyl]-propionic acid pyrrolidide is obtained from the subsequent fractions. Recrystallisation from acetone gives a pure product having a melting point of from 178 to 180°C.

The starting material can be manufactured as follows:

A mixture of 172 g (0.6 mol) of the hydrochloride of 3-(1,2-dicarboxyethyl)-imidazol[1,2-a]-pyridin-2-(3H)-one, 65.5 g (0.78 mol) of 3-methyl-3-buten-2-one, 220 ml of methanol and 220 ml of water is stirred at room temperature for 36 hours and then concentrated to dryness by evaporation *in vacuo* at approximately 45°C. The resulting crude product is taken up in 400 ml of glacial acetic acid, 22.5 g of sodium acetate are added and the whole is boiled under reflux until the evolution of CO_2 is complete. The solvent is then removed *in vacuo*, a mixture of 225 ml of 6M sulphuric acid and 225 ml of tetrahydrofuran is added to the residue and the whole is heated under reflux for 8 hours. After the removal of the tetrahydrofuran *in vacuo*, the reaction mixture is diluted with water and extracted with methylene chloride. The crude product remaining after the organic phase has been dried and concentrated by evaporation is chromatographed with petroleum ether/ether over silica gel. Subsequent distillation (100°C/$8 \cdot 10^{-2}$ mm Hg) gives 4-methyl-3-(2-methyl-3-oxobutyl)-maleic acid anhydride in the form of a pale yellow oil.

Example 3

A mixture of 19.8 g (0.1 mol) of 4-methyl-3-(2-methyl-3-oxobutyl)-maleic acid anhydride and 23.0 g (0.11 mol) of morpholinium benzoate in 400 ml of benzene is heated under reflux on a water separator for 60 hours. The benzene is removed *in vacuo* and the residue is partitioned between methylene chloride and saturated sodium bicarbonate solution. Continuation of the process, as described in Example 2, gives 3,5-dimethyl-6-morpholinobenzofuran-2(3H)-one having a melting point of from 108 to 109°C and 2-(2-hydroxy-5-methyl-4-morpholinophenyl)-propionic acid morpholide having a melting point of from 183 to 185°C.

Example 4

9.5 g (0.035 mol) of 5-chloro-3-methyl-6-morpho-linobenzofuran-2(3H)-one are added to a solution of 0.9 g (0.039 mol) of sodium in 100 ml of methanol. After 3 hours at room temperature the reaction mixture is concentrated to dryness by evaporation *in vacuo* and the residue is dissolved in 50 ml of dimethyl sulphoxide. 5.7 g (0.04 mol) of methyl iodide are added dropwise thereto while stirring. After 16 hours at room temperature, 300 ml of water and 100 ml of hexane are added to the solution and the precipitate that has formed is filtered off. The filtrate is extracted several times with hexane. After evaporation of the hexane, a crystalline residue is obtained. The crude crystals are recrystallised from isopropyl ether. 2-(5-chloro-2-methoxy-4-morpholinophenyl)-propionic acid methyl ester is obtained in the form of colourless crystals having a melting point of from 88 to 89°C.

Example 5

5.4 g (0.02 mol) of 5-chloro-3-methyl-6-morpholinobenzofuran-2(3H)-one are added to a solution of 0.5 g of sodium (0.022 mol) in 50 ml of methanol and the reaction mixture is allowed to stand for 3 hours at room temperature. The reaction mixture is then concentrated to dryness by evaporation *in vacuo*; the residue is dissolved in cold water and washed with ether. The aqueous phase is rendered acidic to Congo Red with dilute hydrochloric acid, while cooling with ice, and extracted with ether. After evaporation of the ether, colourless crystals are obtained which are recrystallised from methanol. 2-(5-chloro-2-hydroxy-4-morpholinophen-yl)-propionic acid methyl ester having a melting point of from 148 to 149°C is obtained.

Example 6

2.0 g (0.023 mol) of morpholine are added to a solution of 5.4 g (0.02 mol) of 5-chloro-3-methyl-6-morpholinobenzofuran-2(3H)-one in 25 ml of ether. After 3 hours, the precipitate which has formed is filtered off, colourless crystals, 2-(5-chloro-2-hydroxy-4-morpholinophenyl)-propionic acid morpholide, having a melting point of from 198 to 199°C being obtained.

Example 7

6 g (0.019 mol) of 2-(5-chloro-2-methoxy-4-morpholinophenyl)-propionic acid methyl ester are boiled under reflux for 2 hours in 100 ml of 2N hydrochloric acid. The reaction mixture is then adjusted to pH 2.5 with dilute sodium hydroxide solution and extracted several times with ether. After the evaporation of the ether, crystals are obtained which are recrystallised from ethyl acetate/petroleum ether (1:1). 2-(5-chloro-2-methoxy-4-morpholinophenyl)-propionic acid is thus obtained in the form of rough prisms having a melting point of from 164 to 165°C.

Example 8

A suspension of 3.0 g (0.01 mol) of 2-(5-chloro-2-hydroxy-4-morpholinophenyl)-propionic acid methyl ester and 0.03 g of 4-dimethylaminopyridine in 30 ml of acetic acid anhydride are heated for 5 minutes on a water bath at 50°C and dissolved. After 1 hour at room temperature the whole is concentrated to dryness by evaporation *in vacuo* and the residue is chromato-

graphed with methylene chloride over silica gel. Colourless crystals are obtained which are recrystallised from isopropyl ether. 2-(2-acetoxy-5-chloro-4-morpholinophenyl)-propionic acid methyl ester having a melting point of from 104 to 105°C is thus obtained.

Example 9

A solution of 11.07 g (30 mmol) of 5-chloro-2-methoxy-4-(piperidin-1-yl)-phenylthioacetic acid morpholine amide in 120 ml of glacial acetic acid and 30 ml of concentrated hydrochloric acid is boiled under reflux for 22 hours. The reaction mixture is cooled, diluted with water and extracted with methylene chloride. The combined methylene chloride phases are washed with water, dried over sodium sulphate and concentrated by evaporation using a high-vacuum rotary evaporator. After chromatography over silica gel with chloroform/methanol (19:1), 5-chloro-2-methyoxy-4-(piperidin-1-yl)-phenylacetic acid, which, after recrystallisation with methylene chloride/hexane, melts at from 120 to 122°C, is obtained.

In analogous manner, 5-chloro-2-methoxy-4-(4-morpholino)-phenylacetic acid having a melting point of from 141 to 143°C is obtained.

The starting material can be manufactured as follows:

Under a nitrogen atmosphere and while cooling with ice/methanol, a solution of 96 g (0.72 mol) of aluminium trichloride in 180 ml of absolute nitromethane is added dropwise, in the course of approximately 30 minutes, to a mixture of 106.2 g (0.60 mol) of 3,4-dichloroanisole [H. Jamarlik *et al.* Comptes Rendus Acad. Sci. Ser. C *273* (25), 1756 (1971)] and 51.1 ml (0.72 mol) of acetyl chloride in such a manner that the internal temperature range is between 0 and 5°C. Stirring is then continued for a further 1 hour at approximately 4 to 6°C, the whole is then poured onto ice and extracted with methylene chloride. The organic extracts are washed with water, combined, dried over sodium sulphate and concentrated by evaporation using a vacuum rotary evaporator. After recrystallisation from methanol/water, 4,5-dichloro-2-methoxyacetophenone having a melting point of from 93 to 95°C is obtained.

A solution of 76.7 g (0.35 mol) of 4,5-dichloro-2-methoxyacetophenone in 750 ml of piperidine is maintained at 170°C for 7 hours in an autoclave. The reaction mixture is concentrated by evaporation, taken up in ethyl acetate and washed with water. The ethyl acetate extracts are combined, dried over sodium sulphate and concentrated by evaporation using a vacuum rotary evaporator. The residue is chromatographed with methylene chloride over silica gel. 5-chloro-2-hydroxy-4-(N-piperidino)-acetophenone having a melting point of from 68 to70°C is thus obtained.

In analogous manner, 5-chloro-2-hydroxy-4-(N-morpholino)-acetophenone having a melting point of from 102 to 103°C is obtained.

A solution of 32.5 g (128 mmol) of 5-chloro-2-hydroxy-4-(N-piperidino)-acetophenone with 75 ml (168 mmol) of an approximately 40% methanolic solution of benzyl triethylammonium hydroxide (Triton B) in 65 ml of tetrahydrofuran is cooled to 0°C. In the course of approximately 6 minutes, 14.6 ml (154 mmol) of dimethyl sulphate are added dropwise in such a manner that the internal temperature does not exceed 5°C. The reaction mixture is stirred for a further 1 hour at 0° and then boiled under reflux for approximately 30 minutes. The reaction mixture is then poured into 400 ml of water and extracted with ethyl acetate. The combined ethyl acetate phases are washed with water, dried over sodium sulphate and concentrated by evaporation using a vacuum rotary evaporator. The residue is recrystallised from methylene chloride/hexane and 5-chloro-2-methoxy-4-(N-piperidino)-acetophenone having a melting point of from 119 to 120°C is obtained.

In analogous manner, 5-chloro-2-methoxy-4-(N-morpholino)-acetophenone having a melting point of from 143 to 145°C is obtained.

A solution of 18.2 g (68 mmol) of 5-chloro-2-methoxy-4-(piperidin-1-yl)-acetophenone and 4.36 g (136 mmol) of sulphur in 68 ml of morpholine is maintained at 90°C for 5 hours. The reaction mixture is cooled, diluted with ethyl acetate and washed with water. The combined ethyl acetate extracts are dried over sodium sulphate and concentrated by evaporation using a vacuum rotary evaporator. After recrystallisation from methylene chloride/methanol, 5-chloro-2-methoxy-4-(piperidin-1-yl)-phenylthioacetic acid morpholine amide having a melting point of from 137 to 139°C is obtained.

In analogous manner, 5-chloro-2-methoxy-4-(4-morpholino)-phenylthioacetic acid morpholine amide having a melting point of from 160 to 162.5°C is obtained.

Example 10

A solution of 8.5 g (30 mmol) of 5-chloro-2-methoxy-4-(4-piperidin-1-yl)-phenylacetic acid in 150 ml of 48% hydrobromic acid is boiled under reflux for 15 hours. The reaction mixture is cooled, diluted with water and the pH is adjusted to from 3 to 4 with saturated sodium bicarbonate solution. The whole is then extracted with ethyl acetate, the combined organic phases are washed with water, dried over sodium sulphate and concentrated by evaporation using a high-vacuum rotary evaporator. A dark grey foam of 5-chloro-2-hydroxy-4-(piperidin-1-yl)-phenylacetic acid is thus obtained.

2-hydroxy-4-(4-morpholino)-phenylacetic acid is obtained analogously.

Example 11

160 ml of 0.1N NaOH is added in the course of approximately 2 minutes under a nitrogen atmosphere and at room temperature to a solution of 4.03 g (16.0 mmol) of 5-chloro-3-methyl-6-(pyrrolidin-1-yl)-benzofuran-2(3H)-one in 160 ml of methanol, and the reaction mixture is stirred for approximately 60 minutes at room temperature. The solvent is then concentrated and the residue is freeze-dried. The sodium salt of 2-(5-chloro-2-hydroxy-4-(pyrrolidin-1-yl)-phenyl)-propionic acid having a melting point of over 200°C with decomposition is obtained.

In analogous manner, the sodium salt of 2-(5-chloro-2-hydroxy-4-morpholinophenyl)-propionic acid having a melting point of over 200°C (decomposition) is obtained.

Example 12

59 g of 4-methyl-3-(2-methyl-3-oxobutyl)-maleic acid anhydride and 240 g of dibenzylammonium benzoate are heated under reflux in 1000 ml of benzene for 48 hours on a water separator. The reaction mixture is then concentrated to dryness by evaporation *in vacuo* and the residue is chromatographed in methylene chloride over silica gel. The resulting oil crystallises fromisopropyl ether. 2-(4-dibenzylamino-2-hydroxy-5-methyl-phenyl)-propionic acid dibenzyl amide having a melting point of from 140 to 141°C is thus obtained.

The starting material can be manufactured as follows:

A mixture of 172 g (0.6 mol) of the hydrochloride of 3-(1,2-dicarboxyethyl)-imidazo[1,2-a]pyridin-2(3H)-one, 85.5 g (0.78 mol) of 3-methyl-3-buten-2-one, 220 ml of methanol and 220 ml of water is stirred for 36 hours at room temperature and then concentrated to dryness by evaporation *in vacuo* at approximately 45°. The resulting crude product is taken up in 400 ml of glacial acetic acid, 22.5 g of sodium acetate are added and the whole is boiled under reflux until the evolution of CO_2 is complete. The solvent is then removed *in vacuo*, a mixture of 225 ml of 6M sulphuric acid and 225 ml of tetrahydrofuran is added to the residue and the whole is heated under reflux for 8 hours. After removal of the tetrahydrofuran *in vacuo*, the reaction mixture is diluted with water and extracted with methylene chloride. The crude product remaining after the organic phase has been dried and concentrated by evaporation is chromatographed with petroleum ether/ether over silica gel. The subsequent distillation (100°C/8.10^{-2} mm Hg) gives 4-methyl-3-(2-methyl-3-oxobutyl)-maleic acid anhydride in the form of a pale yellow oil.

Example 13

20 g of 2-(4-dibenzylamino-2-hydroxy-5-methyl-phenyl)-propionic acid dibenzyl amide are boiled under reflux in 40 ml of 2N hydrochloric acid and 40 ml of glacial acetic acid for 3 hours. The reaction mixture is then concentrated to dryness by evaporation *in vacuo* and the residue is partitioned between ether and 1N sodium hydroxide solution. By means of acidification to a pH of 1 with hydrochloric acid, and extraction, 2-(4-dibenzylamino-2-hydroxy-5-methylphenyl)-propionic acid, which is chromatographed in methylene chloride over silica gel for the purpose of purification and has a melting point of from 174 to 175°C, is obtained.

Example 14

2.3 g (0.01 mol) of 3,5-dimethyl-6-(pyrrol-1-yl)-benzofuran-2(3H)-one are shaken with 15 ml of 1N sodium hydroxide solution and 50 ml of ether for 5 minutes. The acid is isolated by adjustment of the pH of the sodium hydroxide solution to 1 with concentrated hydrochloric acid and extraction with ether.

After recrystallisation from isopropyl ether/petroleum ether, 2-[2-hydroxy-5-methyl-4-(pyrrol-1-yl)-phenyl]-propionic acid having a melting point of from 73 to 74°C is obtained.

The starting material can be obtained, for example, as follows:

A mixture of 19.6 g (0.1 mol) of 4-methyl-3-(2-methyl-3-oxo-butyl)-maleic acid anhydride and 20 g (0.105 mol) of 3-pyrrolinium benzoate in 250 ml of benzene is heated under reflux for 5 hours on a water separator. The benzene is evaporated off *in vacuo* and the residue is partitioned between ether and saturated sodium bicarbonate solution. The crude product remaining after the organic phase has been dried and concentrated by evaporation is chromatographed over silica gel. Elution with diisopropyl ether and subsequent recrystallisation of the pure fractions from isopropyl ether gives 3,5-dimethyl-6-(pyrrol-1-yl)-3a,6-dihydrobenzofuran-2(3H)-one having a melting point of from 116 to 117°.

Example 15

A mixture of 9.0 g (0.04 mol) of 3,5-dimethyl-6-(pyrrol-1-yl)-benzofuran-2(3H)-one and 2.4 g (0.045 mol) of sodium methoxide in 40 ml of methanol is stirred at room temperature for 90 minutes. The methanol is evaporated off *in vacuo* and the residue is dissolved in 100 ml of

ether. To this solution there is added dropwise, at from 0 to 5°C and within a period of 30 minutes, a solution of 4.5 g (0.057 mol) of acetyl chloride in 25 ml of ether. The reaction mixture is stirred at room temperature for 14 hours and then washed with water and ice-cold 1N sodium hydroxide solution. The neutral parts obtained after evaporation of the ether are chromatographed with a mixture of methylene chloride/hexane (3:1) over silica gel. Recrystallisation of the pure eluates from hexane gives 2-[2-acetoxy-5-methyl-4-(pyrrol-1-yl)-phenyl]-propionic acid methyl ester having a melting point of from 70 to 71°.

Example 16

A mixture of 5.5 g (23.8 mmol) of 3,5-dimethyl-6-(pyrrolidin-1-yl)-benzofuran-2(3H)-one and 1.28 g (23.8 mmol) of sodium methoxide in 40 ml of methanol is stirred for 90 minutes at room temperature. The methanol is removed *in vacuo* and the residue is taken up in 90 ml of tetrahydrofuran. 1.9 ml (26.7 mmol) of acetyl chloride are added dropwise to this mixture at from 0 to 5° in the course of 30 minutes. Stirring is continued for one hour at room temperature, the tetrahydrofuran is removed *in vacuo*, the residue is taken up in methylene chloride and the organic phase is extracted with dilute sodium bicarbonate solution. The crude product obtained after drying and after concentration of the methylene chloride by evaporation is chromatographed with petroleum ether/ether over silica gel. Distillation of the pure fractions in a bulb tube (150°C/6.10^{-2} mm Hg) gives 2-[2-acetoxy-5-methyl-4-(pyrrolidin-1-yl)-phenyl]-propionic acid methyl ester.

Example 17

A solution of 3.0 g (0.035 mol) of chromic acid in 20% sulphuric acid is added dropwise to a solution of 2.7 g (0.01 mol) of 2-(5-chloro-2-hydroxy-4-morpholinophenyl)-propan-1-ol in 20 ml of acetone while stirring, at from 15 to 20°C, within a period of 15 minutes. After the addition of 10 ml of methanol, the whole is filtered and the filtrate is concentrated *in vacuo*. The pH is then adjusted to from 1 to 2 with dilute sodium hydroxide solution and the whole is extracted several times with ether. After drying and after evaporation of the ether, the residue is recrystallised from ether. In this manner 2-(5-chloro-2-hydroxy-4-morpholinophenyl)-propionic acid having a melting point of from 198 to 200° is obtained.

The following material can be obtained, for example, as follows:

2.7 g (0.01 mol) of 5-chloro-3-methyl-6-morpholinobenzofuran-2(3H)-one dissolved in 100 m of absolute ether are added dropwise to a suspension of 0.8 g of lithium aluminium hydride (0.02 mol) in 50 ml of absolute ether within a period of 30 minutes at frm 0 to 5° and under a nitrogen atmosphere, while stirring and cooling with ice. The reaction mixture is then stirred at room temperature for 3 hours. By careful dropwise addition of approximately 10 ml of water while cooling with ice, the lithium aluminium complex is split up. The whole is rendered weakly acid by means of 1N hydrochloric acid and extracted 5 times with chloroform. The resulting crude product is recrystallised from ethyl acetate. In this manner 2-(5-chloro-2-hydroxy-4-morpholinophenyl)-propan-1-ol having a melting point of from 176 to 177° is isolated.

Example 18

3.8 g (0.10 mmol) of sodium borohydride are added, in portions and while stirring, to a methanolic solution of 26.9 g (0.10 mol) of 5-chloro-2-methoxy-4-morpholinoacetophenone, and the whole is stirred for one hour at room temperature. The methanol is concentrated using a vacuum rotary evaporator and the residue is partitioned between dilute hydrochloric acid and methylene chloride. The organic phases are combined, dried over sodium sulphate and concentrated by evaporation. The residue is taken up in 60 ml of absolute methylene chloride and added dropwise in the course of 2 hours under a nitrogen atmosphere to a mixture of 17.8 g (0.15 mol) of thionyl chloride and 120 ml of absolute methylene chloride. Stirring is then continued for a further 1 hour, the solvent is concentrated using a vacuum rotary evaporator, and the residue is partitioned between sodium bicarbonate solution and methylene chloride. The organic phases are washed until neutral, combined, dried over sodium sulphate and concentrated. The residue is taken up in 100 ml of absolute tetrahydrofuran and added dropwise to a suspension of 2.4 g (0.10 mol) of magnesium turnings in 20 ml of absolute tetrahydrofuran in such a manner that the reaction mixture boils slightly under reflux. Boiling is then continued for a further 2 hours under reflux. The solution, which has cooled to room temperature, is carefully added dropwise to approximately 50 g of dry ice covered with a layer of absolute tetrahydrofuran. The reaction mixture is heated to room temperature, acidified with dilute hydrochloric acid and extracted three times with methylene chloride. The organic phases are washed until neutral, combined, dried over sodium sulphate and concentrated using a vacuum isolation evaporator. Recrystallisation of the crude product from ethyl acetate/petroleum ether gives 2-(5-chloro-2-methoxy-4-morpholinophenyl)-propionic acid having a melting point of from 164 to 165°.

Example 19

In a well ventilated fume cupboard, approximately 27 g (1.0 mol) of liquid hydrocyanic acid from a pressure bottle is introduced, with nitrogen, into an ice/sodium chloride-cooled sulphonating flask. In the course of approximately 2 minutes, 134.9 g (0.50 mol) of 5-chloro-2-methoxy-4-morpholinoacetophenone and 250 mg (2.9 mmol) of piperidine are added. After 30 minutes at 0°, the cyanohydrin formed is diluted with 100 ml of ether and passed with nitrogen under pressure into 300 ml of concentrated hydrochloric acid which is cooled with ice/sodium chloride and stirred well. The mixture is then saturated with hydrochloric acid gas and then allowed to stand for approximately 15 hours at room temperature. The amide which has crystallised out is filtered with suction, washed with water and, without purification, boiled under reflux for 3 hours with 750 ml of 20% aqueous potassium hyroxide solution. The reaction mixture is cooled, acidified with 6N hydrochloric acid and extracted 3 times with ether. The ether phases are washed until neutral, combined, dried over sodium sulphate and concentrated using a vacuum rotary evaporator. The resulting crude 2-hydroxy-2-[5-chloro-2-methoxy-4-morpholinophenyl]-propionic acid is added in portions at room temperature to 300 ml of concentrated sulphuric acid. After stirring for approximately 10 minutes, the reaction mixture is poured onto 2 kg of ice and extracted three times with ether. The ether extracts are washed with water until neutral, combined, dried over sodium sulphate and concentrated using a vacuum rotary evaporator. The residue is taken up in 700 ml of methanol, 7 g of palladium on carbon are added and the whole is hydrogenated at room temperature. The catalyst is filtered off and the solvent is concentrated using a vacuum rotary evaporator. Recrystallisation of the crude product from ethyl acetate/petroleum ether gives 2-(5-chloro-2-methoxy-4-morpholinophenyl)-propionic acid having a melting point of from 164 to 165°.

Example 20

A solution of 2.86 g (10.0 mmol) of 5-chloro-2-methoxy-4-morpholinophenylacetic acid in 50 ml of saturated methanolic hydrochloric acid is boiled under reflux for 12 hours. The reaction mixture is concentrated using a vacuum rotary evaporator and the residue is taken up in methylene chloride and washed three times with water. The organic phase is dried over sodium sulphate and concentrated using a vacuum rotary evaporator. The resulting 5-chloro-2-methoxy-4-morpholinophenylacetic acid methyl ester is added in portions while stirring vigorously to a mixture of 514 mg (13 mmol) of sodium amide in 60 ml of liquid ammonia. 2.84 g (20 mmol) of methyl iodide are then added dropwise. The whole is stirred for 2 hours and the ammonia is then evaporated off. The residue is partitioned between dilute hydrochloric acid and ether. The ether phases are dried over sodium sulphate and concentrated by evaporation. Recrystallisation of the residue from isopropyl ether gives 2-(5-chloro-2-methoxy-4-morpholinophenyl)-propionic acid methyl ester having a melting point of from 88 to 89°.

Example 21

A mixture of 4 g (12.8 mmol) of 5-bromo-3-methyl-6-morpholinobenzofuran-2(3H)-one and 0.7 g (13 mmol) of freshly prepared sodium methoxide in 25 ml of methanol is stirred for 45 minutes at room temperature. The methanol is removed *in vacuo* and the residue is taken up in 50 ml of tetrahydrofuran. 1.4 ml (19.7 mmol) of acetyl chloride are added dropwise to this mixture at from 0 to 5°C in the course of 2 hours. After the whole has stood at room temperature for 72 hours, the tetrahydrofuran is removed *in vacuo* and the residue is chromatographed with petroleum ether/ether over silica gel. Subsequent recrystallisation of the pure fractions from ether/petroleum ether gives 2-(2-acetoxy-5-bromo-4-morpholinophenyl)-propionic acid methyl ester having a melting point of from 114 to 115°C.

The starting material can be obtained, for example, as follows:

A mixture of 11 g (0.069 mol) of bromine in 50 ml of chloroform is added dropwise to a solution of 15 g (0.064 mol) of 3-methyl-6-morpholinobenzofuran-2(3H)-one in 120 ml of chloroform at from 0 to 5°C, while stirring, in the course of one hour. Stirring is then continued at room temperature for 30 minutes. Methylene chloride is added to the reaction mixture and the whole is washed successively with 10% sodium thiosulphate solution, dilute sodium bicarbnate solution and water. The crude product remaining after the organic phase has been dried and concentrated by evaporation is chromatographed with petroleum ether/ether over silica gel. After recrystallisation of the pure fractions from ether/petroleum ether, 5-bromo-3-methyl-6-morpholinobenzofuran-2(3H)-one having a melting point of from 99 to 100°C is obtained.

Example 22

12.4 g of palladium on carbon is added to a solution of 132.9 g (0.759 mol) of 4-methyl-3-nitroanisole in 1.1 litre of methanol and the reaction mixture is hydrogenated at room temperature. The catalyst is filtered off and the filtrate is concentrated using a vacuum rotary evaporator. Recrystallisation from isopropanol/water gives 3-amino-4-methylanisole having a melting point of from 43 to 44°.

A solution of 88.4 g (0.64 mol) of 3-amino-4-methylanisole in 1.4 litre of glacial acetic acid is heated to 105°, and 114 g (0.88 mol) of 2,5-dimethoxytetrahydrofuran are added at this temperature in the course of 30 minutes. The whole is immediately cooled to room temperature and concentrated using a vacuum rotary evaporator. Distillation of the residue using a high vacuum gives 4-methyl-3-(pyrrol-1-yl)-anisole, which has a boiling point of from 93 to 95°/0.04 mm Hg. R_f (toluene/ethyl acetate = 10:1):0.57.

A solution of 86.6 g (0.46 mol) of 4-methyl-3-(pyrrol-1-yl)-anisole in 1.5 litres of absolute methylene chloride is cooled with acetone/dry ice to −78°. At this temperature, 231.7 g (0.92 mol) of boron tribromide are added dropwise. The cooling bath is then removed and the reaction mixture is heated to from 0 to 5° and then poured into 2 litres of ice/water and the methylene chloride phase is separated off and washed with saturated sodium chloride solution. The aqueous phases are then extracted twice more with methylene chloride. The organic phases are combined, dried over sodium sulphate and concentrated using a vacuum rotary evaporator. Distillation of the residue under a high vacuum gives 4-methyl-3-(pyrrol-1-yl)-phenol, which has a boiling point of from 105 to 107°/0.03 mm Hg, and R_f (toluene/ethyl acetate = 10:1):0.38.

45.7 g (0.39 mol) of crotyl bromide are added to a suspension of 53.4 g (0.31 mol) of 4-methyl-3-(pyrrol-1-yl)-phenol and 53.7 g (0.39 mol) of potassium carbonate in 600 ml of absolute acetone under reflux in the course of 1 hour and boiling is then continued for a further 4½ hours. The reaction mixture is cooled and diluted with 800 ml of water. The acetone is evaporated off using a vacuum rotary evaporator and the residue is extracted several times with methylene chloride. The organic phases are washed with water, combined and dried over sodium sulphate and concentrated using a vacuum rotary evaporator. Quick filtration over approximately 800 g of silica gel with methylene chloride gives 1[4-methyl-3-(pyrrol-1-yl)]-phenyoxy-2-butene in the form of a light yellow oil, R_f (hexane/ether = 9:1):0.45, R_f (toluene/ethyl acetate = 10:1):0.68.

A solution of 60 g (0.26 mol) of 1-[4-methyl-3-(pyrrol-1-yl)-phenoxy-2-butene in 170 ml of absolute N,N-diethylaniline is boiled under reflux for 5 hours. The reaction mixture is cooled, diluted with methylene chloride and acidified with 6N hydrochloric acid. The aqueous phase is separated off and extracted again with methylene chloride. The organic phases are washed until neutral, combined, dried over sodium sulphate and concentrated using a vacuum rotary evaporator. Chromatography over silica gel with hexane/ether (9:1) gives 3-[2-hydroxy-5-methyl-4-(pyrrol-1-yl)-phenyl]-1-butane. R_f (hexane/ether = 9:1):0.17, R_f (toluene/ethyl acetate = 10:1):0.45.

A few drops of pyridine are added to a solution of 26.7 g (0.12 mol) of 3-[2-hydroxy-5-methyl-4-(pyrrol-1-yl)-phenyl]-1-butene in 370 ml of acetic acid anhydride and the whole is stirred for 2 hours at room temperature. The reaction mixture is poured onto ice and extracted 3 times with methylene chloride. The methylene chloride phases are washed with dilute sodium bicarbonate solution, and then with water until neutral, combined, dried over sodium sulphate and concentrated using a vacuum rotary evaporator. Filtration over a small amount of silica gel with methylene chloride gives 3-[2-acetoxy-5-methyl-4-(pyrrol-1-yl)-phenyl]-1-butene, R_f (toluene/ethyl acetate = 10:1):0.55.

A solution of 2.7 g (10 mmol) of 3-[2-acetoxy-5-methyl-4-(pyrrol-1-yl)-phenyl]-1-butene in 40 ml of absolute methylene chloride is cooled with acetone/dry ice to −78° and ozone is blown through until the blue colour no longer disappears. 2 ml of dimethyl sulphide are then added and the cooling bath is removed. The reaction mixture is carefully concentrated using a vacuum rotary evaporator, the residue is dissolved in 50 ml of ethanol and a solution of 3.7 g (23 mmol) of silver nitrate in 5 ml of water is added. A solution of 75 ml of a 1N potassium hydroxide solution is added dropwise to this mixture in the course of approximately 15 minutes. The heterogeneous mixture is stirred for a further 2 hours. The reaction mixture is filtered and the residue is washed with ethanol. The alkaline filtrate is allowed to stand overnight at room temperature and extracted with methylene chloride. The alkaline solution is carefully acidified with 6N hydrochloric acid while cooling and is extracted several times with methylene chloride. The organic phases are washed twice more with water, combined, dried over sodium sulphate and concentrated using a vacuum rotary evaporator. Recrystallisation from diisopropyl ether/petroleum ether gives 2-[2-hydroxy-5-methyl-4-(pyrrol-1-yl)-phenyl]-propionic acid having a melting point of from 73 to 74°.

Example 23

42.6 ml (0.6 mol) of acetyl chloride are added dropwise to 81.1 g (0.5 mol) of 4-methyl-2-(1-methyl-2-propenyl)-phenol at room temperature, while stirring, in the course of 1 hour. The reaction mixture is then heated to 100° and left at this temperature for 2 hours. After cooling, water is carefully added and the whole is extracted with methylene chloride. The organic phase is dried over sodium sulphate and concentrated by evaporation. Subsequent distillation of the remaining residue (64–70°/4 × 10^{-2} mm Hg) gives 4-methyl-2-(1-methyl-2-propenyl)-phenyl acetate in the form of a pale yellow oil.

42.8 g (0.2 mol) of sodium periodate are added in portions to a mixture of 20.4 (0.1 mol) of 4-methyl-2-(1-methyl-2-propenyl)-phenyl acetate and 100 mg (0.4 mmol) of osmium tetroxide in 300 ml of dioxane and 100 ml of water in the course of 30 minutes and the whole is then stirred for one hour. The resulting precipitate is filtered off and rinsed wih dioxane/water (1:1). The aqueous-organic phase is concentrated *in vacuo* to approximately one third and extracted with methylene chloride. The oily crude product obtained after drying and after removal of the methylene chloride is taken up in 100 ml of acetone and oxidised by adding dropwise a solution of 7.2 g (72 mmol) of chromium trioxide and 6.2 ml of concentrated sulphuric acid in 40 ml of water in the course of half an hour. 3 ml of methanol and 200 ml of water are then added, the acetone is removed *in vacuo*, the aqueous phase is extracted with ether and the ether solution is extracted 3 times with 10% sodium hydroxide solution. The alkaline aqueous solution is allowed to stand at room temperature for 3 hours, the pH is then adjusted to 3 with concentrated hydrochloric acid and the whole is extracted with ether. The oil obtained after drying and after removal of the ether is stirred for 2 hours with 300 ml of saturated methanolic hydrochloric acid. The methanol is then removed *in vacuo* and the residue is partitioned between ether and dilute sodium bicarbonate solution. The crude product obtained after the organic phase has been dried and concentrated by evaporation is chromatographed with methylene chloride over silica gel. Subsequent recrystallisation of the pure fractions from methylene chloride/petroleum ether gives 2-(2-hydroxy-5-methylphenyl)-propionic acid methyl ester having a melting point of from 104 to 108°.

A mixture of 5.8 g (30 mmol) of 2-(2-hydroxy-5-methylphenyl)-propionic acid methyl ester, 36.5 g (82 mmol) of lead tetraacetate and 150 ml of glacial acetic acid is stirred at room temperature for 36 hours. The glacial acetic acid is removed *in vacuo* and 300 ml of water are added to the residue. The resulting precipitate is filtered off and washed thoroughly with ether. The filtrate is extracted with ether. The combined ether phases are dried over sodium sulphate and concentrated by evaporation *in vacuo*. The remaining reddish oil is taken up in 80 ml of dioxane, 8.7 ml (106 mmol) of pyrrolidine are added and the whole is boiled under reflux for 5 hours. The dioxane is removed *in vacuo* and the residue is chromatographed with methylene chloride/acetone over silica gel. After recrystallisation of the pure fractions from acetone, 2-[2-hydroxy-5-methyl-4-(pyrrolidin-1-yl)-phenyl]-propionic acid pyrrolidide having a melting point of from 178 to 180° is obtained.

Example 24

A mixture of 19.6 g (0.1 mol) of 4-methyl-3-(2-methyl-3-oxo-butyl)-maleic acid anhydride and 48.2 g of indolinium benzoate in 52 ml of benzene is heated under reflux for 6 hours on a water separator. The benzene is then evaporated off *in vacuo* and the residue is partitioned between ether and 1N hydrochloric acid. The organic phase is washed with saturated sodium bicarbonate solution and, after being dried, is concentrated. The resulting crude (2-[5-methyl-2-hydroxy-4-(indolin-1-yl)-phenyl]-propionic acid indolinyl amide melts at from 176 to 178°.

Example 25

44 g of 2-(4-dibenzylamino-2-hydroxy-5-methyl-phenyl)-propionic acid dibenzyl amide are dissolved in 450 ml of dioxane and, with 10 g of palladium on carbon (5%), are reduced at room temperature and under normal pressure with hydrogen. The reaction mixture is then filtered, the filtrate is concentrated to dryness by evaporation and the residue is recrystallised from ethyl acetate. In this manner 2-(4-amino-2-hydroxy-5-methyl-phenyl)-propionic acid dibenzyl amide having a melting point of from 166 to 167° is obtained.

3.7 g (0.01 mol) of 2-(4-amino-2-hydroxy-5-methylphenyl)-propionic acid dibenzyl amide are suspended in 20 ml of dioxane and, while stirring at room temperature, 2 ml of 2,5-dimethoxytetrahydrofuran and 1.4 ml of 37% hydrochloric acid are added. After 30 minutes, the solvent is removed *in vacuo* and the residue is partitioned between ether and water. The organic phase is washed with saturated sodium bicarbonate solution, dried and concentrated to dryness by evaporation. The residue is chromatographed with methylene chloride over silica gel. Recrystallisation of the pure eluates from isopropyl ether gives 2-[2-hydroxy-5-methyl-4-(pyrrol-1-yl)-phenyl]-propionic acid dibenzyl amide having a melting point of from 150 to 151°.

The starting material can be manufactured as follows: 59 g of 4-methyl-3-(2-methyl-3-oxo-butyl)-maleic acid anhydride and 240 g of dibenzylammonium benzoate are boiled under reflux in 1000 ml of benzene for 48 hours using a water separator. The whole is then concentrated to dryness by evaporation *in vacuo* and the residue is chromatographed over silica gel. The resulting oil crystallises from isopropyl ether. 2-(4-dibenzylamino-2-hydroxy-5-methylphenyl)-propionic acid dibenzyl amide having a melting point of from 140 to 141° is obtained.

Example 26

In an analogous manner as described in example 14 2-[2-hydroxy-5-methyl-6-(2,5-dimethyl-pyrrol-1-yl)-phenyl]-propionic acid is obtained.

The starting material can be manufactured as follows.

5.3 g (0.03 mol) of 6-amino-3,5-dimethylbenzofuran-2(3H)-one, 4.1 g (0.037 mol) of acetonyl acetone, 50 ml of benzene and 0.5 ml of glacial acetic acid are heated under reflux for 14 hours. After cooling, the reaction mixture is washed with water, saturated sodium bicarbonate solution and 1N hydrochloric acid. The benzene is then evaporated off *in vacuo* and the residue is chromatographed with methylene chloride over silica gel. After crystallisation of the pure eluates, 3,5-dimethyl-6-(2,5-dimethyl-pyrrol-1-yl)-benzofuran-2(3H)-one having a melting point of from 94 to 95° is obtained.

Example 27

3.0 g (0.01 mol) of 2-(5-chloro-2-methoxy-4-morpholinophenyl)-propionic acid are heated under reflux in 20 ml of 48% hydrobromic acid for 1 hour. The reaction mixture is then concentrated to dryness by evaporation *in vacuo*, the residue is dissolved in dilute sodium hydroxide solution, the pH is adjusted to from 1 to 2 with dilute hydrochloric acid and the whole is extracted several times with ether. After drying and after evaporation of the ether, the crude acid, which can be recrystallised from a small amount of ether, is obtained. In this manner 2-(5-chloro-2-hydroxy-4-morpholinophenyl)-propionic acid having a melting point of from 198 to 200° is obtained.

Example 28

Tablets containing 25 mg of active ingredient, for example 2-(5-chloro-2-hydroxy-4-morpholinophenyl)-propionic acid methyl ester or a salt thereof, for example, the hydrochloride, can be manufactured in the following manner:

Constituents (for 1000 tablets):

Active ingredient	25.0 g
Lactose	100.7 g
Wheat starch	7.5 g
Polyethylene glycol 6000	5.0 g
Talc	5.0 g
Magnesium stearate	1.8 g
Demineralised water	q.s.

Manufacture

All the solid ingredients are first forced through a sieve having a mesh width of 0.6 mm. Then the active ingredient, the lactose, the talc, the magnesium stearate and half the starch are mixed together. The other half of the starch is suspended in 40 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 ml of water. The resulting starch paste is added to the main batch and the mixture is granulated, if necessary with the addition of water. The granules are dried overnight at 35°C, forced through a sieve having a mesh width of 1.2 mm and pressed to give tablets which are concave on both sides and have a diameter of approximately 8 mm.

Example 29

Chewable tablets containing 30 mg of active ingredient, for example the sodium salt of 2-(5-chloro-2-hydroxy-4-(pyrrolidin-1-yl)-phenyl)-propionic acid or a salt, for example the hydrochloride, thereof, can be manufactured, for example, in the following manner:

Composition (for 1000 tablets):

Active ingredient	30.0 g
Mannitol	267.0 g
Lactose	179.5 g
Talc	20.0 g
Glycine	12.5 g
Stearic acid	10.0 g
Saccharin	1.0 g
5% gelatin solution	q.s.

Manufacture

All the solid ingredients are first forced through a sieve having a mesh width of 0.25 mm. The mannitol and the lactose are mixed, granulated with the addition of the gelatin solution, forced through a sieve having a mesh width of 2 mm, dried at 50°C and again forced through a sieve having a mesh width of 1.7 mm. The active ingredient, the glycine and the saccharin are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and

the whole is thoroughly mixed and pressed to give tablets that are concave on both sides and have a diameter of approximately 100 mm and a breaking groove on the upper side.

Example 30

Tablets containing 100 mg of active ingredient, for example the sodium salt of 2-(5-chloro-2-hydroxy-4-morpholinophenyl)-propionic acid or a salt thereof, for example the hydrochloride, can be manufactured in the following manner:

Composition (for 1000 tablets):

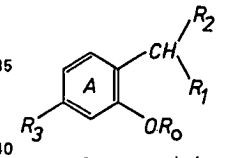
Active ingredient	100.0 g
Lactose	248.5 g
Corn starch	17.5 g
Polyethylene glycol 6000	5.0 g
Talc	15.0 g
Magesium stearate	4.0 g
Demineralised water	q.s.

Manufacture

The solid ingredients are first forced through a sieve having a mesh width of 0.6 mm. Then the active ingredient, lactose, talc, magnesium stearate and half the starch are intimately mixed. The other half of the starch is suspended in 65 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 ml of water. The resulting paste is added to the pulverulent substances and the whole is mixed and granulated, if necessary with the addition of water. The granules are dried overnight at 35°C, forced through a sieve having a mesh width of 1.2 mm and pressed to give tablets that are concave on both sides and have a diameter of approximately 10 mm and a breaking groove on the upper side.

CLAIMS

1. Phenol derivatives of the general formula



(I),

in which R_o represents hydrogen or an acyl radical, R_1 represents carboxy, esterified carboxy or amidated carboxy, R_2 represents hydrogen or an aliphatic radical, R_3 represents an amino group di-substituted by two monovalent hydrocarbon radicals or by one divalent hydrocarbon radical, and the aromatic ring A may be additionally substituted, and their salts and isomers.

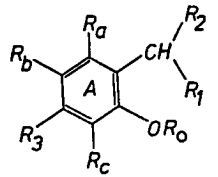
2. Compounds of the formula (I) according to claim 1, in which R_o represents hydrogen, a lower alkanoyl radical or an aryl-lower alkanoyl radical, R_1 represents carboxy, carboxy esterified by an aliphatic or aromatic alcohol, carbamoyl or mono- or di-substituted carbamoyl, R_2 represents a saturated and unsubstituted aliphatic radical, R_3 represents an amino group di-substituted by two monovalent aliphatic radicals or an amino group di-substituted by a divalent aliphatic radical, and the aromatic ring A may be additionally mono- or poly-substituted by an aliphatic radical, lower alkoxy, lower alkylthio, lower alkanesulphinyl, lower alkanesulphonyl, hydroxy, halogen, lower alkanoyloxy, lower alkanoyl and/or nitro or, except for R_3, it may be unsubstituted, and their salts, especially pharmaceutically acceptable salts, and isomers.

3. Compounds of the formula (I) according to claim 1, in which R_o represents hydrogen, lower alkanoyl or phenyl-lower alkanoyl in which the phenyl radical may be unsubstituted or mono- or polysubstituted by lower alkyl, hydroxy-lower alkyl, halo-lower alkyl, lower alkenyl, 3- or 4-membered alkylene, lower alkoxy, lower alkylthio, lower alkanesulphinyl, lower alkanesulphonyl, hydroxy, halogen, lower alkanoyloxy, lower alkanoyl and/or nitro, or phenyl-lower alkanoyl deriving from a phenyl-lower alkanecarboxylic acid of the formula (I) in which R_o is hydrogen or lower alkanoyl and R_2 and R_3 as well as the substituents of the ring A have the meanings given below, R_1 represents carboxy, lower alkoxycarbonyl, hydroxy-lower alkoxycarbonyl, lower alkanoyloxy-lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl, phenoxycarbonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, N-mono- or N,N-di-phenyl-lower alkylcarbamoyl, N-mono- or N,N-diphenylcarbamoyl, N-lower alkyl-N-phenyl-lower alkylcarbamoyl, N-lower alkyl-N-phenylcarbamoyl, N-phenyl-lower alkyl-N-phenylcarbamoyl, lower alkylenecarbamoyl, or

lower alkylenecarbamoyl or lower alkenylenecarbamoyl each interrupted by monoaza, N'-lower alkylmonoaza, monooxa or monothia, wherein phenyl and phenoxy may in each case be unsubstituted or mono- or poly-substituted by lower alkyl, hydroxy-lower alkyl, halo-lower alkyl, lower alkenyl, 3- or 4-membered alkylene, lower alkoxy, lower alkythio, lower alkanesulphinyl, lower alkanesulphonyl, hydroxy, halogen, lower alkanoyloxy, lower alkanoyl and/or nitro, lower alkylene or lower alkenylene having one or two ortho-fused benzo systems and/or being branched or unbranched, R_2 represents hydrogen or lower alkyl and R_3 represents, on the one hand, N,N-di-lower alkylamino, N-cyclo-lower alkyl-N-lower alkylamino, N-lower alkyl-N-phenyl-lower alkylamino, N,N-dicyclo-lower alkyl-lower alkylamino, N-cyclo-lower alkyl-lower alkyl-N-phenyl-lower alkylamino or N,N-diphenyl-lower alkylamino or, on the other hand, in each case 5- to 8-membered lower alkyleneamino, lower alkenyleneamino, lower alkyleneamino interrupted by monoaza, N'-lower alkylmonoaza, monooxa or monothia, lower alkenyleneamino interrupted by monoaza, N'-lower alkylmonoaza, monooxa or monothia, or lower alkyleneamino or lower alkenyleneamino containing one or two ortho-fused benzo systems, wherein lower alkylene and lower alkenylene may also be branched and may contain from 4 to 14, especially from 4 to 7, carbon atoms, and/or having one or two ortho-fused benzo systems, and phenyl or benzo may each be unsubstituted or mono- or poly-substituted by lower alkyl, hydroxy-lower alkyl, halo-lower alkyl, lower alkenyl, 3- or 4-membered alkylene, lower alkoxy, lower alkylthio, lower alkanesulphinyl, lower alkanesulphonyl, hydroxy, halogen, lower alkanoyloxy, lower alkanoyl and/or nitro, and the aromatic ring A may be mono- or poly-substituted by lower alkyl, hydroxy-lower alkyl, halo-lower alkyl, lower alkenyl, 3- or 4-membered alkylene, lower alkoxy, lower alkylthio, lower alkane sulphinyl, lower alkane-sulphonyl, hydroxy, halogen, lower alkanoyloxy, lower alkanoyl and/or nitro or, except for R_3, it may be unsubstituted, and their salts, especially pharmaceutically acceptable salts, and isomers.

4. Compounds of the formula (I) according to claim 1, in which R_a represents hydrogen, lower alkanoyloxy or phenyl-lower alkanoyloxy the phenyl moiety of which is unsubstituted or mono-or poly-substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy and/or trifluoromethyl, R_1 represents carboxy; carboxy esterified by a lower alkanol, by a lower alkanol substituted by hydroxy, lower alkoxy, lower alkanoyloxy or phenyl the phenyl moiety of which is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy and/or trifluoromethyl, or by a phenol that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy and/or trifluoromethyl; carbamoyl; carbamoyl that is mono-substituted by lower alkyl, or by phenyl-lower alkyl the phenyl moiety of which is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy and/or trifluoromethyl; or carbamoyl that is di-substituted by lower alkyl, by phenyl-lower alkyl the phenyl moiety of which is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy and/or trifluoromethyl, by lower alkylene, or by lower alkylene that is interrupted by monoaza, N-alkylated monoaza, monooxa or monothia, R_2 represents hydrogen or lower alkyl, R_3 represents an amino group di-substituted by lower alkyl, by 3 to 7-membered cycloalkyl-lower alkyl, by phenyl-lower alkyl the phenyl moiety of which is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy and/or trifluoromethyl, by lower alkylene, by lower alkenylene, by lower alkylene interrupted by aza, N-lower alkylaza, oxa or thia, or by lower alkenylene interrupted by aza or N-lower alkylaza, and the aromatic ring A may be additionally substituted by lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyoloxy, 3- or 4-membered alkylene and/or trifluoromethyl, and their salts, especially pharmaceutically acceptable salts, and isomers.

5. Compounds according to claim 1 of the formula



(Ia),

in which R_a represents hydrogen or lower alkanoyl, R_1 represents carboxy, lower alkoxycarbonyl, lower alkylenecarbamoyl or oxa-lower alkylene-carbamoyl, R_2 represents hydrogen or lower alkyl, R_3 represents di-lower alkylamino, dicycloalkyl-lower alkylamino, diphenyl-lower alkylamino, 5-to 8-membered lower alkyleneamino, 5- to 8-membered lower alkenyleneamino, 5- to 8-membered monoaza-lower alkyleneamino, 5- to 8-membered N'-lower alkylmonoaza-lower alkyleneamino, 5- to 8-membered monooxa-lower alkyleneamino, 5- to 8-membered monothia-lower alkylene-

amino, 5- to 8-membered monoaza-lower alkenyleneamino, or 5- to 8-membered N'-lower alkylmonoaza-lower alkenyleneamino and each of R_b, R_b and R_c, independently of one another, represents hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, lower alkanoyloxy, 3- or 4-membered alkylene, or trifluoromethyl, and their salts, especially pharmaceutically acceptable salts, and isomers.

6. Compounds of the formula (Ia) according to claim 1, in which R_a represents hydrogen or lower alkanoyl, or phenyl-lower alkanoyl deriving from a phenyl-lower alkanecarboxylic acid of the formula (I), in which R_a is hydrogen and R_2, R_3, R_b, R_b and R_c have the meanings given below, R_1 represents carboxy, lower alkoxycarbonyl, lower alkanoyloxy-lower alkoxycarbonyl, carbamoyl, N,N-diphenyl-lower alkylcarbamoyl, lower alkylenecarbamoyl, or lower alkylene-carbamoyl interrupted by monooxa, R_2 represents hydrogen or lower alkyl, R_3 represents, on the one hand, N,N-di-phenyl-lower alkylamino or, on the other hand, 5- to 8-membered lower alkyleneamino, 5- to 8-membered lower alkenyleneamino, 5- to 8-membered lower alkyleneamino interrupted by monooxa, or 5- to 8-membered lower alkylene-amino or lower alkenyleneamino respectively having one ortho-fused benzo system, and/or each of R_b, R_b and R_c, independently of one another, represents hydrogen, lower alkyl or halogen, and their salts, especially pharmaceutically acceptable salts, and isomers.

7. Compounds of the formula (Ia) according to claim 1, in which R_a represents hydrogen or lower alkanoyl, R_1 represents carboxy, lower alkoxycarbonyl, 5- to 8-membered lower alkylene-cabamoyl, or 5- to 8-membered monooxa-lower alkylenecarbamoyl, R_2 represents hydrogen or lower alkyl, R_3 represents di-lower alkylamino, 5- to 8-membered lower alkyleneamino, 5- to 8-membered lower alkenylene-amino, or 5- to 8-membered monooxa-lower alkyleneamino, each of R_b and R_b represents hydrogen and R_b represents halogen, and their salts, especially pharmaceutically acceptable salts, and isomers.

8. Compounds of the formula (Ia) according to claim 1, in which R_a represents hydrogen or lower alkanoyl having up to and including 5 carbon atoms, R_1 represents carboxy or lower alkoxycabonyl having up to and including 5 carbon atoms, R_2 represents lower alkyl having up to and including 4 carbon atoms, R_3 represents 5- to 7-membered lower alkyleneamino, morpholin-4-yl or pyrrol-1-yl, each of R_b and R_b represents hydrogen and R_b represents lower alkyl having up to and including 4 carbon atoms, or halogen having an atomic number of up to and including 35, and their salts, especially phamaceutically acceptable salts, and isomers.

9. Compounds of the formula (Ia) according to claim 1, in which R_a represents lower alkanoyl having up to and including 5 carbon atoms, R_1 represents lower alkoxy-carbonyl having up to and including 5 carbon atoms, R_2 represents lower alkyl having up to and including 4 carbon atoms, R_3 represents morpholin-4-yl or pyrrol-1-yl, each of R_b and R_b represents hydrogen, and R_b represents halogen having an atomic number of up to and including 35, or lower alkyl having up to and including 4 carbon atoms, and their salts, especially pharmaceutl-cally acceptable salts, and isomers.

10. 2-(5-Chloro-3-methyl-6-morpholino-phenyl)-propionic acid or a salt or isomer thereof.

11. 2-[2-Hydroxy-5-methyl-4-(pyrrolidin-1-yl)-phenyl]-propionic acid pyrrolide or a salt or isomer thereof.

12. 2-(2-Hydroxy-5-methyl-4-morpholino-phenyl)-propionic acid morpholide or a salt or isomer thereof.

13. 2-(5-Chloro-2-hydroxy-4-morpholino-phenyl)-propionic acid methylester or a salt or isomer thereof.

14. 2-(5-Chloro-2-hydroxy-4-morpholino-phenyl)-propionic acid morpholide or a salt or isomer thereof.

15. 2-(2-Acetoxy-5-chloro-4-morpholino-phenyl)-propionic acid methylester or a salt or isomer thereof.

16. 5-Chloro-2-hydroxy-4-(piperidin-1-yl)-phenylacetic acid or a salt or isomer thereof.

17. 2-[5-Chloro-2-hydroxy-4-(pyrrolidin-1-yl)-phenyl]-propionic acid-sodium salt or an isomer thereof.

18. 2-(5-Chloro-2-hydroxy-4-morpholino-phenyl)-propionic acid-sodium salt or an isomer thereof.

19. 2-(4-Dibenzylamino-2-hydroxy-5-methyl-phenyl)-propionic acid dibenzylamie or a salt or isomer thereof.

20. 2-(4-Dibenzylamino-2-hydroxy-5-methyl-phenyl)-propionic acid or a salt or isomer thereof.

21. 2-[2-Hydroxy-5-methyl-4-(pyrrol-1-yl)-phenyl]-propionic acid or a salt or isomer thereof.

22. 2-[Acetoxy-5-methyl-4-(pyrrol-1-yl)-phenyl]-propionic acid methylester or a salt or isomer thereof.

23. 2-[2-Acetoxy-5-methyl-4-(pyrrolidin-yl)-phenyl]-propionic acid methylester or a salt or isomer thereof.

24. 2-(2-Acetoxy-5-bromo-4-morpholino-phenyl)-propionic acid methylester or a salt or isomer thereof.

25. 2-[2-Hydroxy-5-methyl-4-(pyrrol-1-yl)-phenyl]-propionic acid pyrrolide or a salt or isomer thereof.

26. 2-[5-Methyl-2-hydroxy-4-(indolin-1-yl)-phenyl]-propionic acid indolinyl amide or a salt or isomer thereof.

27. 2-[2-Hydroxy-5-methyl-(pyrrol-1-yl)-phenyl]-propionic acid dibenzylamide or a salt or isomer thereof.

28. Compound according to any one of claims 2, 3, 6, 8 and 21–27 having anti-inflammatory and/or analgesic action.

29. Compound according to any one of claims 1, 4, 5, 7 and 9–20 having anti-inflammatory and/or analgesic action.

30. Compound according to any one of claims 1–27 acting as light-screening agent.

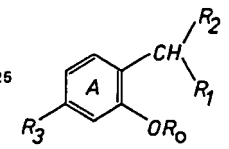
31. The novel compounds mentioned in Examples 14 to 27.

32. The novel compounds mentioned in Examples 1 to 13.

33. Compound according to any one of claims 1 to 29 for the therapeutic treatment of the human or animal body.

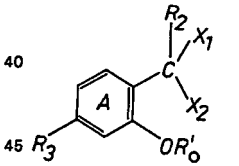
34. Pharmaceutical preparations containing a compound according to any one of claims 1 to 29 in addition to customary pharmaceutical adjuncts and carriers.

35. Process for the manufacture of phenol derivatives, especially those of the general formula



(I),

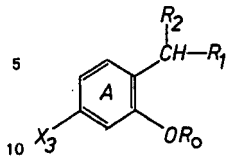
in which R_o represents hydrogen or an acyl radical, R_1 represents carboxy, esterified carboxy or amidated carboxy, R_2 represents hydrogen or an aliphatic radical, R_3 represnts an amino group di-substituted by two monovalent hydrocarbon radicals or by one divalent hydrocarbon radical, and the aromatic ring A may be additionally substituted, and their salts and isomers, characterised in that compounds of the formula



(II),

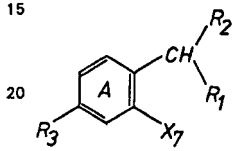
in which X_1 is hydrogen, X_2 represents functionally modified carboxy that is different from R_1, and R'_o has the same meaning as R_o, or in which X_1 is hydrogen and X_2 together with R'_o forms the group

or in which X_1 together with X_2 forms the group $=C=O$ or the group $=C(Hal)_2$, Hal in each case representing halogen, and R'_o has the same meaning as R_o, or salts thereof, are treated with solvolysis agents or in compounds of the formula



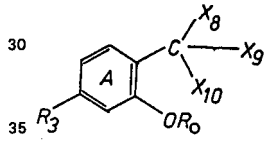
(III)

or salts thereof in which X_3 represents a radical that can be converted ino R_3, X_3 is converted into R_3 or in compounds of the formula



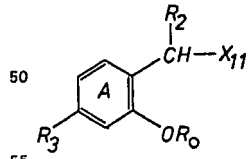
(IV)

in which X_7 represents a radical that can be converted into the group $-OR_o$, the radical X_7 is converted into the group $-OR_o$ or compounds of the formula



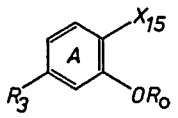
(V)

or salts thereof in which each of X_8 and X_9 represents carboxy and X_{10} has the same meaning as R_2; in which X_8 has the same meaning as R_1, X_9 has the same meaning as R_2 and X_{10} represents hydroxy, functionally modified hydroxy, mercapto substituted by a hydrocarbon radical or secondary amino; in which X_8 has the same meaning as R_1 and X_9 and X_{10} together represent oxo, thioxo or optionally substituted hydrazonon, or in which X_8 has the same meaning as R_1 and X_9 and X_{10} together form the group $=R'_2$ or a tautomeric form thereof, and R'_2 represents a divalent aliphatic radical are converted by reduction into the corresponding compound of the formua (I) or in compounds of the formula



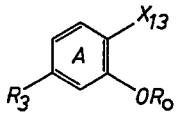
(VI)

or salts thereof in which X_{11} represent a radical that can be converted into R_1 by oxidation, X_{11} is converted into R_1 by oxidation or in a compound of the formula



(VIII)

or a salt thereof in which X_{15} represents a radical that can be converted into a group of the formula $-CH(R_2)-R_1$. X_{15} is converted into a group of the formula $-CH(R_2)-R_1$ by rearrangement or in a compound of the formula



(VII)

in which X_{13} represents a radical that can be converted into a group of the formula $-CH(R_2)-R_1$ (VIIa), or in a salt or isomer thereof, the radical X_{13} is converted into a group of the formula $-CH(R_2)-R_1$, and if desired, converting a salt obtainable according to the process into the free compound or into a different salt, converting a free compound obtainable according to the process into a salt or into a different free compound, and/or, if desired, separating an isomeric mixture obtainable according to the process into its components.

36. Use of compounds according to any one of claims 1 to 29 in a method for the treatment of inflammatory and/or rheumatic diseases and/or painful conditions.

37. The process of Example 1 to 27 and the novel compounds obtainable thereby.

38. The novel starting materials and intermediates used in the process according to claim 35.

Printed for Her Majesty's Stationery Office by Burgess & Son (Abingdon) Ltd.—1983.
Published at The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.